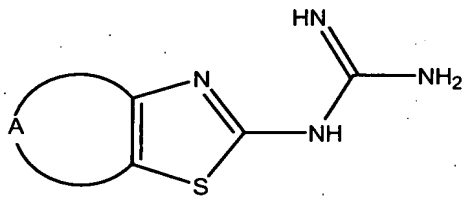
GUANIDINE DERIVATIVES AND THEIR USE AS NEUROPEPTIDE FF RECEPTOR ANTAGONISTS

The present invention relates to guanidine derivatives of the general formula



I

in which A represents a chain of 3-6 optionally substituted C atoms, one of which can be replaced by -N(R')- or -O-; and R' represents hydrogen or a substituent; the ring skeleton containing only the two double bonds of the thiazole component; pharmaceutically applicable acid addition salts of basic compounds of formula I, pharmaceutically applicable salts of acid group-containing compounds of formula I with bases, pharmaceutically applicable esters of hydroxy or carboxy group-containing compounds of formula I as well as hydrates or solvates thereof.

Guanidine derivatives of formula I which contain one or more asymmetric centres can be present as optically pure enantiomers, as mixtures of enantiomers, such as for example racemates, or optionally as optically pure diastereomers, as mixtures of diastereomers, as diastereomeric racemates or as mixtures of diastereomeric racemates.

The products defined at the outset are partly known and partly novel, and they are characterized by valuable pharmacodynamic properties, acting as neuropeptide FF receptor antagonists.

In a first aspect the present invention relates to the use of the compounds described at the outset of Formula I as well as the salts, esters, hydrates and solvates likewise defined at the outset as neuropeptide FF receptor antagonists or for the preparation of corresponding medicinal products, in particular for the treatment of pain and hyperalgesia, withdrawal syndromes in the case of alcohol, psychotropic and nicotine

dependences and for the improvement or elimination of these dependences, for the regulation of insulin secretion, food intake, memory functions, blood pressure, and of the electrolyte and energy balance and for the treatment of urinary incontinence or for the preparation of corresponding medicinal products.

The pains to be treated according to the invention can be chronic, acute, long-lasting or temporary, these pains being able to be of operative, traumatic, or pathological origin; an advantage achieved according to the invention consists in the prevention of opioid tolerance and/or opioid dependence.

Back in 1985 neuropeptide FF (NPFF; H-Phe-Leu-Phe-Gln-Pro-Gln-Arg-Phe-NH_2 [99566-27-5]), an octapeptide, and neuropeptide AF (NPAF; H-Ala-Gly-Glu-Gly-Leu-Ser-Ser-Pro-Phe-Trp-Ser-Leu-Ala-Ala-Pro-Gln-Arg-Phe-NH_2 [99588-52-0]), a related octadecapeptide, were discovered as neurotransmitters of the central nervous system in cattle brains (Yang et al., Proc. Natl. Acad. Sci. USA 1985, 82(22), 7757-61) and originally characterized as anti-opioid peptides. The carboxy-terminal amidated neuropeptides were, because of their reactivity with anti-Phe-Met-Arg-Phe-NH_2 antiserum, included among the FMRF-amide-like peptides. Both peptides have pain-modulating properties, the octapeptide having greater effectiveness. Both peptides play an important role both in opioid-dependent analgesia and in the development of tolerance to opioids (review article: Roumy and Zajac, Europ. J. Pharm. 1998, 345, 1-11; Panula et al., Prog. Neurobiol. 1996, 48, 461-87). Interestingly, in animal tests, NPFF shows, depending on the nature of the administration, both anti-opioid and pro-opioid actions. Thus NPFF can reverse the acute effects of opioids and an increased concentration in the brain is possibly responsible for the development of opioid tolerance and dependence. In rats, for example, the intracerebroventricular (i.c.v.) administration of NPFF lowers the nociceptive threshold and reduces the analgesia induced by morphine. Administration of NPFF to morphine-tolerant rats causes symptoms of withdrawal phenomena. The analgesic effect of morphine in morphine-tolerant rats was reproduced after i.c.v. injection of anti-NPFF IgG (Lake et al., Neurosci. Lett. 1991, 132, 29-32). Immunoneutralization of NPFF by intrathecally (i.t.) administered anti-NPFF antibodies increase the analgesia caused by endogenous and

exogenous opioids. By direct injection of NPFF or NPFF-analogues into the spinal cord (i.t.) a pro-opioid effect with a long-lasting opioid-like analgesia and an increased pain-relieving effect of morphine was obtained (Gouardères et al., Eur. J. Pharmacol. 1993, 237, 73-81; Kontinen and Kaso, Peptides 1995, 16, 973-977).

According to other reports NPFF also appears to play a role in physiological processes such as insulin secretion, regulation of food intake, memory functions, regulation of blood pressure and electrolyte balance (Panula et. al., Prog. Neurobiol. 1996, 48, 461-487).

In various types of mammal, such as humans, rats, mice and cattle, the discovery was reported of a gene, which codes NPFF and NPAF as a common precursor protein, from which the two active peptides are finally split off (Perry et al., FEBS Lett. 1997, 409, 426-30; Vilim et al., Mol. Pharmacol. 1999, 55, 804-11). In humans the gene for this precursor is expressed both peripherally in various organs and in regions of the central nervous system, in particular in the cerebellum (Elshourbagy et al., J. Biol. Chem. 2000, 275 (34), 25965-71), while the expression in rats is restricted exclusively to specific regions of the central nervous system such as the hypothalamus, medulla, and dorsal horn of the spinal cord. On the basis of the demonstration of NPFF in human blood plasma it is presumed, that the peptides are peripherally also responsible for hormone-like effects (Sandblom et al., Peptides 1998, 19, 1165-70).

In tissue samples from humans and rats two G-protein coupled receptors (GPCR), NPFF1 and NPFF2 were identified (Bonini et al., J. Biol. Chem. 2000, 275 (50), 39324-31; Kotani et al., Br. J. Pharmacol. 2001, 133, 138-44), NPFF2 being identical to the receptor HLWAR77 originally described as an orphan (Elshourbagy et al., J. Biol. Chem. 2000, 275 (34), 25965-71). NPFF1 and NPFF2 were able to be characterized as specific receptors with affinities in the nanomolar and subnanomolar regions for the two neuropeptides FF and AF. NPFF binds to NPFF1 with a binding constant Kd = 1.13 nM and to NPFF2 with Kd = 0.37 nM. The identity of NPFF1 and NPFF2 is around 50%. The comparison of the amino acid sequences with known GPCRs shows a 30-40% similarity with human orexin-1, orexin-2, neuropeptide Y(NPY) Y2, cholecystokinin A,

NPY Y1, prolactin-releasing hormone receptor and NPY Y4. The distribution of NPFF1 and NPFF2 in various tissue samples from humans and rats was determined by demonstrating the m-RNA using RT-PCR (reverse transcription-polymerase chain reaction). NPFF1 was demonstrated predominantly in the central nervous system (CNS). By contrast, NPFF2 was found predominantly in the spinal cord. These findings are supported by autoradiographic methods using selective NPFF1 and NPFF2 radioligands (Allard et al., Brain Res. 1989, 500, 169-176; Neuroscience 1992, 49, 106-116; Gouardères et al., Neuroscience 2002 115:2 349-61).

The neuropeptides SF (NPSF, 37 amino acids) and neuropeptide VF (NPVF, octapeptide) described as NPFF-related peptides, both located on the so-called NPVF-gene, bind with comparatively greater affinity and selectivity to the NPFF1 receptor than NPFF and NPAV. The NPVF peptides also block the morphine-induced analgesia in acute and inflammatory pain models more markedly than NPFF and emphasize the importance of the NPVF/FF1 system as part of an endogenous anti-opioid mechanism (Q. Liu et al., J. Biol. Chem. 2002,276 (40), 36961).

The incidence of functional NPFF1 and NPFF2 receptors in adipocytes and the effect of NPFF and NPAF on key sites of signal transmission in the adipose metabolism suggest that the two peptides, alongside their original pain-modulating effects, could also have an influence on the storage and use of body energy (I. Lefrère et al., J. Biol. Chem. 2002, 277 (42), 39169).

The desamino-Tyr-Phe-Leu-Phe-Gln-Pro-Gln-Arg-NH_2 peptide was described as the first NPFF-receptor antagonist counteracting the NPFF effects. After i.c.v. injection this peptide reduced the withdrawal syndromes in the case of morphine dependence (Malin et al., Peptides 1991, 12, 1011-1014). However, this peptide showed no bioavailability whatever in the central nervous system. Optimization of the tripeptide Pro-Gln-Arg-NH_2 in a combinative approach led to dansyl-Pro-Gln-Arg-NH_2, or dansyl-Pro-Ser-Arg-NH_2, both with improved properties for passing through the blood-brain barrier, which, after systemic administration in rats led to an improved antagonistic effect of the anti-opioid symptoms caused by NPFF (Prokai et al. J. Med. Chem. 2001, 44, 1623-1626).

The Arg-Tyr-amide peptoid BIBP3226 originally described as an NPY Y1 selective receptor antagonist showed a 10-60 times higher affinity to the human and rat-NPFF1 receptor than to the corresponding NPFF2 receptors (Bonini et al., J. Biol. Chem. 2000, 275 (50), 39324-31). From a series of compounds which originate from the NPY Y1 selective antagonist BIP3226, selective hNPFF1 receptor antagonists were obtained which showed affinities of 40-80 nM (Mollereau et al., Europ. J. Pharmacol. 2002, 45, 245-56).

The two neuropeptide FF analogues 1DME ([D-Tyr^1,(Nme)Phe^3]NPFF) and Nic-1DME (nicotinoyl-pro-1Dme) showed different pharmacological properties in the mouse tail-flick test, although both compounds bind to NPFF1 and NPFF2 with comparable affinity and selectivity. Both 1DME and Nic-1DME reinforce the morphine analgesia after i.t. and i.p. administration, but Nic-1DME cannot suppress morphine-induced analgesia after i.c.v. and i.p. administration (Quelven et al., Europ. J. Pharmacol. 2002, 449, 91-98).

In WO 02/24192 A1 synthetic NPFF ligands with a peptide structure, based on arginine as the central component, are described.

The products defined at the outset are potent and specific, low-molecular antagonists of neuropeptide FF1 receptors with non-peptide or non-peptoid structures.

The current options for treatment of chronic pain are based on NSAIDs (non-steroidal anti-inflammatory drugs), canabinoids and opioids. Thus, for example, morphine derivatives bind to the μ-opioid receptor and thereby have an analgesic effect. Opioid binding to the μ-opioid receptor involves the release of neuropeptide FF. Based on the animal experiments mentioned above it is presumed that the released NPFF reduces the analgesic effect of the administered opioids and leads to tolerance to opioids. In order to obtain a constant analgesic effect with longer treatments, increasingly higher opioid doses must be administered as a result of this tolerance, which can finally lead to serious side effects. As already mentioned at the outset, as of today two neuropeptide

FF receptors are known, the NPFF1 receptor being located mainly in the central nervous system and the NPFF2 receptor in the spinal cord in particular. Activation of the NPFF2 receptors shows an opioid-like analgesic effect. Blocking of the NPPF1 receptors by an antagonist prevents the development of tolerance to opioids and also increases their effect.

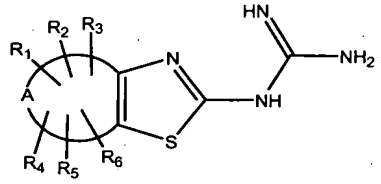
As mentioned at the outset, the products defined there are partly known and partly novel, and they are characterized by the valuable pharmacological property of blocking the interaction of neuropeptide FF with the neuropeptide FF1 receptor subtype.

If one or more of the C atoms in the chain A in formula I is/are substituted, then

- one of the C atoms can carry one or two (i.e. geminal) identical or different substituents; or
- several of the C atoms can each carry one or two (i.e. geminal) identical or different substituents.

In Formula I, A together with the thiazole ring can form a cyclopentathiazole, benzothiazole, cycloheptathiazole, pyranothiazole, thiazolopyridine, thiazoloazepine or thiazolooxepane skeleton which contains only the two double bonds of the thiazole component, such as for example a 4,5,6,7-tetrahydrobenzothiazole, 5,6,7,8-tetrahydro-4H-cycloheptathiazole, 5,6-dihydro-4H-cyclopentathiazole, 6,7-dihydro-4H-pyrano[4,3-d]thiazole, or 5,6,7,8-tetrahydro-4H-thiazolo[4,5-c]azepine skeleton.

A subgroup of the compounds of Formula I can be represented by the general formula



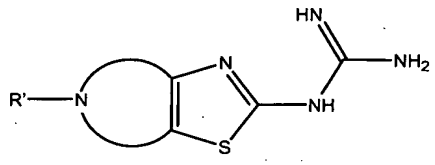
II

in which R_1-R_6 mean hydrogen, alkyl, alkanoyl, alkenyl, alkoxy, alkoxyalkyl, alkoxyalkanoyl, alkoxyalkylcarbamoyl, alkoxyalkylthiocarbamoyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkoxycarbonylalkanoyl, alkylamido, alkylaminocarbonyl, alkylarylamino, alkylcarbamoyl, alkylthiocarbamoyl, alkylcarbonyl, alkylcarbonyloxy,

alkylenedioxy, alkylsulphinyl, alkylsulphinylalkyl, alkylsulphonyl, alkylsulphonylalkyl, alkylthio, alkylsulphonamido, alkylthioalkyl, alkynyl, amino, aminoalkyl, aminoalkanoyl, aminoacyl, alkylamino, alkylaminoalkyl, alkylaminoalkanoyl, aminocarbonyl, aminocarbonylalkyl, aminocarbonylalkanoyl, alkylaminocarbonylamino, alkoxycarbonylamino, aryl, arylalkenyl, arylalkyloxy, arylalkyl, arylalkylamido, arylalkanoyl, arylamido, arylamino, aryl-aminocarbonyl, arylcarbamoyl, arylthiocarbamoyl, aryloxy, aryloxyalkyl, aryloxyalkanoyl, aryloxyalkylamino, aryloxyalkylcarbamoyl, aryloxyalkylthiocarbamoyl, aryloxycarbonyl, aryloxycarbonylalkyl, aryloxycarbonylalkanoyl, aryloxycarbonylalkylamino, aryloxycarbonylalkylcarbamoyl, aryloxycarbonylalkylthiocarbamoyl, arylsulphinyl, arylsulphinylalkyl, arylsulphonyl, arylsulphonylalkyl, arylsulphonylalkanoyl, arylsulphonamido, arylthio, arylthioalkyl, arylthioalkanoyl, carboxy, carboxyl, carboxyalkyl, carboxyalkylamido, cyano, cyanoalkyl, cyanoalkylamido, cyanoalkanoyl, cycloalkyl, cycloalkylamido, cycloalkanoyl, cycloalkylamino, cycloalkylaminocarbonyl, cycloalkyloxycarbonyl, cycloalkyloxycarbonylalkyl, cycloalkyloxy-carbonylalkylamido, cycloalkyloxycarbonylalkanoyl, dialkylaminocarbonyl, dialkylaminoalkyl, dialkylaminoalkylamido, dialkylaminoalkanoyl, diarylamino, formyl, formylalkyl, halogen, haloalkoxy, haloalkyl, haloalkylamido, haloalkanoyl, halo-alkylamino, heteroarylamino, heteroarylamido, heterocyclylalkylamido, heteroarylaminocarbonyl, heteroaryloxycarbonylalkyl, heteroaryloxycarbonylalkylamido, hetero-aryloxycarbonylalkanoyl, heterocyclyl, heterocyclylamino, heterocyclylamido, heterocyclylalkyl, heterocyclylalkanoyl, heterocyclylalkylamino, heterocyclylalkylamido, heteroarylalkyl, heteroarylalkanoyl, heteroarylalkylamino, heteroarylalkylamido, heteroyclylalkylaminocarbonyl, heterocyclylalkoxycarbonylalkyl, heterocyclylalkoxy-carbonylalkanoyl, heterocyclylalkoxycarbonylalkylamino, heterocyclylalkoxycarbonylalkylamido, hydroxy, hydroxyalkyl, hydroxyalkanoyl, mercapto or nitro.

Preferred possible meanings for R_1 are methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, *tert*-butyl, 1,1-dimethylpropyl, or phenyl. If R_2-R_6 are different from hydrogen, then they preferably mean methyl or another low alkyl radical.

Another subgroup of the compounds of Formula I can be represented by the general Formula



III

in which R' means alkyl, alkanoyl, alkenyl, alkinyl, alkoxycarbonylalkyl, alkoxycarbonylaminoalkanoyl, alkylcarbamoyl, alkoxycarbonylalkylcarbamoyl, alkoxycarbonylalkylthiocarbamoyl, alkylthiocarbamoyl, mono- or disubstituted aminoalkanoyl, aryl, arylalkyl, arylalkoxycarbonyl, arylalkanoyl, arylcarbamoyl, alkoxyalkanoyl, alkylsulphonyl, arylthiocarbamoyl, aryloxycarbonylalkyl, aryloxycarbonylalkanoyl, aryloxycarbonylalkylcarbamoyl, aryloxycarbonylalkylthiocarbamoyl, arylsulphonyl, cycloalkyl, cycloalkanoyl, cycloalkylcarbamoyl, cycloalkylthiocarbamoyl, cycloalkylcarbonyl, cycloalkyloxycarbonylalkyl, cycloalkyloxycarbonylalkanoyl, cycloalkyloxycarbonylalkylcarbamoyl, cycloalkyloxycarbonylalkyl-thiocarbamoyl, heteroarylalkyl, heterocyclylalkyl, heterocyclylalkoxycarbonylalkyl, heterocyclylalkoxycarbonylalkanoyl, heterocyclylalkoxycarbonylalkylcarbamoyl, heterocyclylalkoxycarbonylalkylthiocarbamoyl, heteroaryloxycarbonylalkyl, heteroaryloxycarbonylalkylcarbamoyl or heteroaryloxycarbonylalkylthiocarbamoyl.

R' preferably means methyl, ethyl, propyl, hexyl, 2,2-dimethylpropionyl, cyclopropylmethyl, 2-cyclohexylethyl, propinyl, ethyloxycarbonylethyl, benzyl, n-butyloxycarbonyl, *tert*-butyloxycarbonyl, benzyloxy-carbonyl, 3-methyl-butyryl, pentanoyl, phenylacetyl, 2-propyl-pentanoyl, cyclopropanecarbonyl, isobutyryl, but-3-enoyl, 2-methoxy-acetyl, propane-2-sulphonyl, butane-1-sulphonyl, methanesulphonyl, *tert*-butyloxycarbonyl-aminopropionyl or 4-dimethylamino-butyryl.

The use according to the invention of the following compounds of Formula III is preferred:

2-guanidino-6,7-dihydro-4*H*-thiazolo[5,4-c]pyridine-5-carboxylic acid *tert*-butyl ester;
N-(5-hexyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine-2-yl)-guanidine;
N-[5-(2-cyclohexyl-ethyl)-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine-2-yl]-guanidine;
N-(5-ethyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine-2-yl)-guanidine;
2-guanidino-6,7-dihydro-4*H*-thiazolo[5,4-c]pyridine-5-carboxylic acid butyl ester;
N-[5-(propane-2-sulphonyl)-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine-2-yl]-guanidine;
N-(5-phenylacetyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine-2-yl)-guanidine;
2-guanidino-6,7-dihydro-4*H*-thiazolo[5,4-c]pyridine-5-carboxylic acid benzyl ester;
N-(5-pentanoyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine-2-yl)-guanidine;
2-guanidino-6,7-dihydro-4*H*-thiazolo[5,4-*c*]pyridine-5-thiocarboxylic acid propyl amide;
N-[5-(2-propyl-pentanoyl)-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine-2-yl]-guanidine;
N-(5-benzyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine-2-yl)-guanidine;
N-(5-prop-2-ynyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine-2-yl)-guanidine;
N-(5-cyclopropanecarbonyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine-2-yl)-guanidine;
N-[5-(butane-1-sulphonyl)-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine-2-yl]-guanidine;
N-(5-isobutyryl-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine-2-yl)-guanidine;
N-[5-(2,2-dimethyl-propionyl)-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine-2-yl]-guanidine;
2-guanidino-6,7-dihydro-4*H*-thiazolo[5,4-*c*]pyridine-5-thiocarboxylic acid benzyl amide;
2-guanidino-6,7-dihydro-4*H*-thiazolo[5,4-*c*]pyridine-5-carboxylic acid *tert*-butyl amide;
N-(5-but-3-enoyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine-2-yl)-guanidine;
N-(5-benzyl-5,6,7,8-tetrahydro-4*H*-thiazolo[4,5-c]azepine-2-yl)-guanidine;
3-(2-guanidino-6,7-dihydro-4*H*-thiazolo[5,4-c]pyridine-5-yl)-propionic acid ethyl ester;
2-guanidino-6,7-dihydro-4*H*-thiazolo[5,4-*c*]pyridine-5-carboxylic acid pentyl amide;
N-[5-(2-methoxy-acetyl)-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine-2-yl]-guanidine;
N-(5-cyclopropylmethyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine-2-yl)-guanidine;
N-(5-methanesulphonyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine-2-yl)-guanidine;
N-[5-(3-methyl-butyryl)-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine-2-yl]-guanidine;
2-guanidino-6,7-dihydro-4*H*-thiazolo[5,4-*c*]pyridine-5-thiocarboxylic acid-(2-methoxy-1-methyl-ethyl)-amide;

2-guanidino-6,7-dihydro-4*H*-thiazolo[5,4-*c*]pyridine-5-carboxylic acid phenyl amide;
[3-(2-guanidino-6,7-dihydro-4*H*-thiazolo[5,4-c]pyridine-5-yl)-3-oxo-propyl]-carbamic acid *tert*-butyl ester;
N-[5-(4-dimethylamino-butyryl)-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine-2-yl]-guanidine;
N-(5-propyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine-2-yl)-guanidine; and
2-guanidino-6,7-dihydro-4*H*-thiazolo[5,4-*c*]pyridine-5-thiocarboxylic acid isopropyl amide.

Compounds of the Formula I defined at the outset in which A means a chain of 3-6 optionally substituted C atoms, one of which can be replaced by -O-, the ring skeleton containing only the two double bonds of the thiazole component;
pharmaceutically applicable acid addition salts of basic compounds, pharmaceutically applicable salts of acid group-containing compounds with bases, pharmaceutically applicable esters of hydroxy or carboxy group-containing compounds as well as hydrates or solvates thereof;
with the exception of

- N-(4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine;
- (2-guanidino-4,5,6,7-tetrahydro-benzothiazole-4-yl)-ethyl acetate ethyl ester;
- N-(4-hydroxymethyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine;
- N-(4-tosyloxymethyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine;
- N-(4-azidomethyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine;
- N-(4-aminomethyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine; and
- N-(6-acetylaminomethyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine;

are novel.

In a further aspect the present invention thus comprises these novel substances as such and as therapeutic active ingredients; methods for their preparation; medicinal products, containing one of the above novel substances; the preparation of such medicinal products; and the use of these novel substances as neuropeptide FF receptor antagonists or for the preparation of corresponding medicinal products according to the first aspect described above of the present invention.

In the novel compounds defined above of Formula I, in chain A

- one of the C atoms can carry one or two (i.e. geminal), identical or different substituents; or
- several of the C atoms can each carry one or two (i.e. geminal), identical or different substituents.

The substituent(s) can be selected from
alkyl, alkenyl, cycloalkenyl, aryl, heteroaryl, aralkyl, alkoxycarbonyl, carboxamido, cyano or cyanolakyl groups and/or from polymethyl groups linked with one and the same C atom.

In particular the substituent(s) can be selected from

- methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, *sec*-butyl, *tert*-butyl, 1,1-dimethylpropyl, allyl and cyclohex-1-enyl groups; and/or
- phenyl, o-tolyl, m-tolyl, p-tolyl, 2-ethylphenyl, 3-fluorophenyl, 4-fluorophenyl, 4-chlorophenyl, 4-cyanophenyl, 4-benzyloxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 3,4-dimethoxyphenyl, 3,4-methylenedioxyphenyl and bis-3,5-trifluoromethylphenyl groups; and/or
- thiophene-2-yl and benzyl groups; and/or
- ethoxycarbonyl groups; and/or
- n-propylamino, benzylamino, N-methyl-N-phenethylamino, 3-methylbutylamino, phenylamino, N-butyl-N-ethylamino, di-n-propylamino, allylamino, piperidine-1 and morpholine-4-carbonyl groups; and/or
- cyano and cyanoethyl groups; and/or
- pentamethylene groups linked with one and the same C atom.

Novel compounds are preferred in which there is located on one and the same C atom on the one hand a phenyl group and on the other hand an ethoxycarbonyl, cyano or phenyl group.

Quite particularly preferred novel substances are:

N-(5-ethyl-5-methyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine and its formate;
N-(5,5-dimethyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine and its formate;
N-(5,5-dimethyl-6-phenyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine and its formate;
N-(4-*tert*-butyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine;
N-(6-isopropyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine;
N-(5,5,7-trimethyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine;
N-(6,6-dimethyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine;
N-(5-butyl-5,6,7,8-tetrahydro-4*H*-cycloheptathiazol-2-yl)-guanidine;
N-(4-ethyl-4-methyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine;
N-[6-(3,4-dimethoxyphenyl)-4,5,6,7-tetrahydro-benzothiazole-2-yl]-guanidine and its formate;
N-(5-butyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine;
N-(6-phenyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine;
N-(5-methyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine;
N-(4-methyl-4-propyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine;
N-(6-propyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine;
N-(4-cyclohex-1-enyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine and its formate;
N-(4-*sec*-butyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine and its formate; and
N-(4-isobutyl-4-methyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine.

Other particularly preferred novel substances are:
N-(6-*tert*-butyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine;
2-guanidino-6-phenyl-4,5,6,7-tetrahydro-benzothiazole-6-carboxylic acid ethyl ester and its formate;
N-[6-(1,1-dimethyl-propyl)-4,5,6,7-tetrahydro-benzothiazole-2-yl]-guanidine;
N-(7-methyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine and its formate;
N-[6-(3-methoxy-phenyl)-4,5,6,7-tetrahydro-benzothiazole-2-yl]-guanidine and its formate;
N-(6-thiophene-2-yl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine and its formate;
N-(5,5,7,7-tetramethyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine;

N-[6-(4-fluorophenyl)-4,5,6,7-tetrahydro-benzothiazole-2-yl]-guanidine and its hydrobromide;

2-guanidino-4,5,6,7-tetrahydro-benzothiazole-6-carboxylic acid ethyl ester and its hydrobromide;

N-(4,4-dimethyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine;

N-(4-methyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine and its formate;

N-(4,5,6,7-tetrahydro-benzothiazole-2-yl-4-spiro-cyclohexane)-guanidine and its formate;

N-(5,6,7,8-tetrahydro-4H-cycloheptathiazol-2-yl)-guanidine;

N-(4-allyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine and its formate;

N-(6-methyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine;

N-[6-(3-fluorophenyl)-4,5,6,7-tetrahydro-benzothiazole-2-yl]-guanidine and its formate;

N-(6-cyano-6-phenyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine and its hydrobromide;

N-(4-phenyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine and its formate; and

N-(6,6-diphenyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine and its formate.

Novel substances which are also preferred are:

N-[6-(4-methoxy-phenyl)-4,5,6,7-tetrahydro-benzothiazole-2-yl]-guanidine and its hydrobromide;

N-(5-phenyl-5,6,7,8-tetrahydro-4*H*-cycloheptathiazol-2-yl)-guanidine and its hydrobromide;

N-(6,7-dihydro-4H-pyrano[4,3-d]thiazol-2-yl)-guanidine;

N-(6-benzo[1,3]dioxol-5-yl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine and its formate;

2-guanidino-4,5,6,7-tetrahydro-benzothiazole-6-carboxylic acid propyl amide and its formate;

N-[6-(4-cyanophenyl)-4,5,6,7-tetrahydro-benzothiazole-2-yl]-guanidine and its formate;

N-(4-benzyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine and its formate;

N-(5-methyl-5-phenyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine and its formate;

N-[6-(3,5-to-trifluoromethylphenyl)-4,5,6,7-tetrahydro-benzothiazole-2-yl]-guanidine and its formate;

N-(6-*o*-tolyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine and its formate;
N-(6-*m*-tolyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine and its formate;
N-[6-(2-ethyl-phenyl)-4,5,6,7-tetrahydro-benzothiazole-2-yl]-guanidine and its formate;
N-[6-(4-chlorophenyl)-4,5,6,7-tetrahydro-benzothiazole-2-yl]-guanidine and its formate;
2-guanidino-4,5,6,7-tetrahydro-benzothiazole-4-carboxylic acid benzyl amide and its formate;
N-(5,6-dihydro-4*H*-cyclopentathiazol-2-yl)-guanidine;
N-[6-(4-benzyloxy-phenyl)-4,5,6,7-tetrahydro-benzothiazole-2-yl]-guanidine and its hydrobromide;
2-guanidino-4,5,6,7-tetrahydro-benzothiazole-4-carboxylic acid methyl phenethyl amide and its formate;
N-(6-phenyl-4,5,6,7-tetrahydro-benzothiazole-2-yl-4-spiro-cyclohexane)-guanidine and its hydrobromide;
N-(6-*p*-tolyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine and its formate
2-guanidino-4,5,6,7-tetrahydro-benzothiazole-4-carboxylic acid-(3-methyl-butyl)-amide and its formate; and
N-(4-*tert*-butyl-6-phenyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine.

Other representative examples of the novel substances are:
2-guanidino-4,5,6,7-tetrahydro-benzothiazole-6-carboxylic acid phenyl amide and its formate;
2-guanidino-4,5,6,7-tetrahydro-benzothiazole-4-carboxylic acid butyl ethyl amide and its formate;
N-[4-(2-cyano-ethyl)-4,5,6,7-tetrahydro-benzothiazole-2-yl]-guanidine and its formate;
2-guanidino-4,5,6,7-tetrahydro-benzothiazole-4-carboxylic acid ethyl ester and its hydrobromide;
2-guanidino-4,5,6,7-tetrahydro-benzothiazole-4-carboxylic acid dipropyl amide and its formate;
2-guanidino-4,5,6,7-tetrahydro-benzothiazole-4-carboxylic acid phenyl amide and its formate;
2-guanidino-4,5,6,7-tetrahydro-benzothiazole-6-carboxylic acid allyl amide and its formate;

2-guanidino-4,5,6,7-tetrahydro-benzothiazole-4-carboxylic acid propyl amide and its formate;

N-[4-(piperidine-1-carbonyl)-4,5,6,7-tetrahydro-benzothiazole-2-yl]-guanidine and its formate;

2-guanidino-4,5,6,7-tetrahydro-benzothiazole-4-carboxylic acid allyl amide and its formate;

2-guanidino-4,5,6,7-tetrahydro-benzothiazole-6-carboxylic acid-(3-methyl-butyl)-amide and its formate;

N-[4-(morpholine-4-carbonyl)-4,5,6,7-tetrahydro-benzothiazole-2-yl]-guanidine and its formate; and

2-guanidino-4,5,6,7-tetrahydro-benzothiazole-4-carboxylic acid diisopropyl amide and its formate.

The term "alkyl", alone or in combination, describes a linear or branched hydrocarbon radical with 1-8 C atoms. Representative, but not limitative, examples of alkyl are methyl, ethyl, n-propyl, isopropyl, n-butyl, *tert*-butyl, isobutyl (or 2-methylpropyl), n-pentyl (or n-amyl), isopentyl (or isoamyl), n-hexyl n-heptyl, n-octyl and the like. The alkyl radical can carry one or more substituents which are selected independently of each other from alkenyl, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkylcarbonyl, alkylcarbonylalkyl, alkylcarbonyloxy, alkylenedioxy, alkylsulphinyl, alkylsulphinylalkyl, alkylsulphonyl, alkylsulphonylalkyl, alkylthio, alkylthioalkyl, alkynyl, amino, aminoalkyl, aminocarbonyl, aminocarbonylalkyl, aryl, arylalkenyl, arylalkyloxy, arylalkyl, aryloxy, aryloxycarbonyl, aryloxycarbonylalkyl, arylsulphinyl, arylsulphinylalkyl, arylsulphonyl, arylsulphonylalkyl, arylthio, arylthioalkyl, carboxy, carboxyalkyl, cyano, cyanoalkyl, formyl, formylalkyl, halogen, haloalkoxy, haloalkyl, heterocyclyl, hydroxy, hydroxyalkyl, mercapto, nitro and the like, and which can be linked with any C atom of the alkyl group.

The term "low alkyl", alone or in combination, describes alkyl groups with 1-4 C atoms. Representative, but not limitative, examples of low alkyl are methyl, ethyl, n-propyl, isopropyl, n-butyl, *tert*-butyl and the like.

The term "alkenyl", alone or in combination, describes a linear or branched hydrocarbon radical of 2-8 C atoms in which at least one carbon-carbon double bond ($R_aR_bC=CR_cR_d$) is present. R_a-R_d describe substituents which are chosen independently of each other from hydrogen, alkyl, alkoxy, alkoxyalkyl, and the like. Representative, but not limitative, examples of alkenyl are ethenyl, 2-propenyl, 2-methyl-2-propenyl, 3-butenyl, 4-pentenyl, 5-hexenyl and the like.

The term "alkylenedioxy", alone or in combination, describes a $-O(CH_2)_nO$ group, in which n means 1 or 2, the O-atoms being bound to two neighbouring C atoms of the main molecule skeleton. Representative, but not limitative, examples of alkylenedioxy are methylenedioxy, ethylenedioxy and the like.

The term "alkynyl", alone or in combination, describes a linear or branched hydrocarbon radical with 2-8 C atoms, in which at least one carbon-carbon triple bond (R_a-C≡C-R_b) is present. R_a and R_b describe substituents which are chosen independently of each other from hydrogen, alkenyl, alkoxy, alkoxyalkyl, and the like. Representative, but not limitative, examples of alkynyl are acetylenyl, 1-propynyl, 2-propynyl, 1-butynyl, 3-butynyl, 2-pentynyl and the like.

The term "alkoxy", alone or in combination, describes an alkyl group which is linked via an oxygen bridge. Representative, but not limitative, examples of alkoxy are methoxy, ethoxy, propoxy, 2-propoxy, butoxy, *tert*-butoxy, pentyloxy, and hexyloxy.

The term "alkoxyalkyl", alone or in combination, describes an alkoxy group which is linked via an alkyl radical. Representative, but not limitative, examples of alkoxyalkyl are *tert*-butoxymethyl, 2-ethoxyethyl, 2-methoxyethyl, and methoxymethyl.

The term "alkoxycarbonyl", alone or in combination, describes an alkoxy group which is linked via a carbonyl group. Representative, but not limitative, examples of alkoxycarbonyl are methoxycarbonyl, ethoxycarbonyl, *tert*-butoxycarbonyl and the like.

The term "alkoxycarbonylalkyl", alone or in combination, describes an alkoxycarbonyl group which is linked via an alkyl radical. Representative, but not limitative, examples of alkoxycarbonylalkyl are methoxycarbonylpropyl, ethoxycarbonylbutyl, 2-*tert*-butoxycarbonylethyl and the like.

The term "alkylcarbonyl", alone or in combination, describes an alkyl group which is linked via a carbonyl group. Representative, but not limitative, examples of alkylcarbonyl are acetyl, 1-oxopropyl, 2,2-dimethyl-1-oxopropyl, 1-oxobutyl, 1-oxopentyl and the like.

The term "alkylcarbonylalkyl", alone or in combination, describes an alkylcarbonyl group which is linked via an alkyl group. Representative, but not limitative, examples of alkylcarbonylalkyl are 2-oxopropyl, 3,3-dimethyl-2-oxopropyl, 3-oxobutyl, 3-oxopentyl and the like.

The term "alkylcarbonyloxy", alone or in combination, describes an alkylcarbonyl group which is linked via an oxygen bridge. Representative, but not limitative, examples of alkylcarbonyloxy are acetyloxy, ethylcarbonyloxy, *tert*-butylcarbonyloxy and the like.

The term "alkylsulphinyl", alone or in combination, describes an alkyl group which is linked via a sulphinyl group. Representative, but not limitative, examples of alkylsulphinyl are methylsulphinyl, ethylsulphinyl and the like.

The term "alkylsulphinylalkyl", alone or in combination, describes an alkylsulphinyl group which is linked via an alkyl group. Representative, but not limitative, examples of alkylsulphinylalkyl are methylsulphinylmethyl, ethylsulphinylmethyl and the like.

The term "alkylsulphonyl", alone or in combination, describes an alkyl group which is linked via a sulphonyl group. Representative, but not limitative, examples of alkylsulphonyl are methylsulphonyl, ethylsulphonyl and the like.

The term "alkylsulphonylalkyl", alone or in combination, refers to an alkylsulphonyl group which is linked via an alkyl group. Representative, but not limitative, examples of alkylsulphonylalkyl are methylsulphonylmethyl, ethylsulphonylmethyl and the like.

The term "alkylthio", alone or in combination, describes an alkyl group which is linked via a thio group. Representative, but not limitative, examples of alkylthio are methylsulphanyl, ethylsulphanyl, *tert*-butylsulphanyl, hexylsulphanyl and the like.

The term "alkylthioalkyl", alone or in combination, describes an alkylthio group which is linked via an alkyl group. Representative, but not limitative, examples of alkylthioalkyl are methylsulphanyl-methyl, 2-(ethylsulphanyl)ethyl and the like.

The term "amino", alone or in combination, describes a $-NR_eR_f$ group, in which R_e and R_f are chosen independently from hydrogen, alkyl, aryl, arylalkyl, acyl, alkylcarbonyl, arylcarbonyl, carbamoyl, ureido, formyl, alkylsulphonyl, arylsulphonyl and the like.

The term "aminoalkyl", alone or in combination, describes an amino group which is linked via an alkyl group. Representative, but not limitative, examples of aminoalkyl are aminomethyl, 2-aminoethyl, N-benzyl-N-methyl-aminomethyl, dimethylamino-methyl and the like.

The term "aminocarbonyl", alone or in combination, describes an amino group which is linked via a carbonyl group. Representative, but not limitative, examples of aminocarbonyl are dimethylaminocarbonyl, benzylaminocarbonyl, ethylaminocarbonyl and the like.

The term "aminocarbonylalkyl", alone or in combination, describes an aminocarbonyl group which is linked via an alkyl group. Representative, but not limitative, examples of aminocarbonylalkyl are 2-amino-2-oxoethyl, 2-(benzylamino)-2-oxoethyl, 2-(methylamino)-2-oxoethyl, 4-amino-4-oxobutyl, 4-(dimethylamino)-4-oxobutyl and the like.

The term "aryl", alone or in combination, describes an aromatic carbocyclic group containing at least one aromatic ring, for example phenyl or biphenyl, or condensed ring systems in which at least one ring is aromatic, for example 1,2,3,4-tetrahydronaphthyl, naphthyl, anthryl, phenanthryl, fluorenyl and the like. The aryl group can carry one or more substituents which are chosen independently of each other from alkenyl, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylcarbonyl, alkylcarbonylalkyl, alkylcarbonyloxy, alkylenedioxy, alkylsulphinyl, alkylsulphinylalkyl, alkylsulphonyl, alkylsulphonylalkyl, alkylthio, alkylthioalkyl, alkynyl, amino, aminoalkyl, aminocarbonyl, aminocarbonylalkyl, arylalkenyl, arylalkyloxy, arylalkyl, aryloxy, aryloxycarbonyl, aryloxycarbonylalkyl, arylsulphinyl, arylsulphinylalkyl, arylsulphonyl, arylsulphonylalkyl, arylthio, arylthioalkyl, carboxy, carboxyalkyl, cyano, cyanoalkyl, formyl, formylalkyl, halogen, haloalkoxy, haloalkyl, heterocyclyl, hydroxy, hydroxyalkyl, mercapto, nitro and the like.

The term "arylalkenyl", alone or in combination, describes an aryl group which is linked via an alkenyl group. Representative, but not limitative, examples of arylalkenyl are 2-phenylethenyl, 3-phenylpropen-2-yl, 2-naphth-2-ylethenyl and the like.

The term "arylalkoxy", alone or in combination, describes an aryl group which is linked via an alkoxy group. Representative, but not limitative, examples of arylalkoxy are 2-phenylethoxy, 5-phenylpentyloxy, 3-naphth-2-ylpropoxy and the like.

The term "arylalkyl", alone or in combination, describes an aryl group which is linked via an alkyl group. The aryl group can be unsubstituted or substituted. Representative, but not limitative, examples of arylalkyl are benzyl, 2-phenylethyl, 3-phenylpropyl, 2-naphth-2-ylethyl and the like.

The term "aryloxy", alone or in combination, describes an aryl group which is linked via an oxygen bridge. The aryl group can be unsubstituted or substituted. Representative, but not limitative, examples of aryloxy are phenoxy, naphthyloxy, 3-bromophenoxy, 4-chlorophenoxy, 4-methylphenoxy, 3,4-dimethoxyphenoxy and the like. The aryl group can be unsubstituted or substituted as defined.

The term "carbamoyl", alone or in combination, describes a $-C(O)NR_eR_f$ group.

The term "thiocarbamoyl", alone or in combination, describes a $-C(S)NR_eR_f$ group.

The term "carbonyl", alone or in combination, describes a –C(O)- group.

The term "carboxy", alone or in combination, describes a $-CO_2H$ group.

The term "carboxyalkyl", alone or in combination, describes a carboxy group which is linked via an alkyl group. Representative, but not limitative, examples of carboxyalkyl are carboxymethyl, 2-carboxyethyl, 3-carboxypropyl and the like.

The term "cyano", alone or in combination, describes a –C≡N- group.

The term "cyanoalkyl", alone or in combination, describes a cyano group which is linked via an alkyl group. Representative, but not limitative, examples of cyanoalkyl are cyanomethyl, 2-cyanoethyl, 3-cyanopropyl and the like.

The term "cycloalkyl", alone or in combination, describes a saturated cyclic hydrocarbon radical with 3-15 C atoms which can carry one or more substituents. The substituents are independently selected from alkenyl, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylcarbonyl, alkylcarbonylalkyl, alkylcarbonyloxy, alkylenedioxy, alkylsulphinyl, alkylsulphinylalkyl, alkylsulphonyl, alkylsulphonylalkyl, alkylthio, alkylthioalkyl, alkynyl, amino, aminoalkyl, aminocarbonyl, aminocarbonylalkyl, aryl, arylalkenyl, arylalkyloxy, arylalkyl, aryloxy, aryloxycarbonyl, aryloxycarbonylalkyl, arylsulphinyl, arylsulphinylalkyl, arylsulphonyl, arylsulphonylalkyl, arylthio, arylthioalkyl, carboxy, carboxyalkyl, cyano, cyanoalkyl, formyl, formylalkyl, halogen, haloalkoxy, haloalkyl, heterocyclyl, hydroxy, hydroxyalkyl, mercapto, nitro and the like. Representative, but not limitative, examples of cycloalkyl are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl,

cyclooctyl. In polycyclic cycloalkyl radicals one of the fused rings can be aromatic, such as for example 1-indanyl, 2-indanyl, tetrahydronaphthyl and the like.

The terms "cycloalkenyl" and "cycloalkinyl" describe cyclic hydrocarbon radicals which contain at least one carbon-carbon double or triple bond. Like the cycloalkyl radicals, these radicals can carry one or more substituents.

The term "formyl", alone or in combination, describes a –C(O)H group.

The term "formylalkyl", alone or in combination, describes a formyl group which is linked via an alkyl group. Representative, but not limitative, examples of formylalkyl are formylmethyl, 2-formylethyl, and the like.

The term "halo" or "halogen", alone or in combination, describes fluorine, bromine, chlorine, and iodine.

The term "haloalkyl", alone or in combination, describes an alkyl group in which at least one hydrogen atom is replaced by halogen. Representative, but not limitative, examples of haloalkyl are chloromethyl, 2-fluoroethyl, trifluoromethyl, pentafluoroethyl, 2-chloro-3-fluoropentyl and the like.

The term "haloalkoxy", alone or in combination, describes an alkoxy group in which at least one hydrogen atom is replaced by halogen. Representative, but not limitative, examples of haloalkoxy are chloromethoxy, 2-fluorethoxy, trifluoromethoxy, pentafluoroethoxy and the like.

The term "heterocyclyl", alone or in combination, describes a monocyclic, bicyclic or polycylic ring system with up to 15 ring atoms, containing at least one heteroatom independently chosen from nitrogen, oxygen, or sulphur, the ring(s) being able to be saturated, partially unsaturated or unsaturated or aromatic. Representative, but not limitative, examples of heterocyclyl are furyl, imidazolyl, imidazolinyl, imidazolidinyl,

isothiazolyl, isoxazolyl, morpholinyl, oxadiazolyl, oxazolyl, oxazolinyl, oxazolidinyl, piperazinyl, piperidinyl, pyranyl, pyrazinyl, pyrazolyl, pyridyl, pyrimidinyl, pyridazinyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothienyl, thiadiazolyl, thiazolyl, thiazolinyl, thiazolidinyl, thienyl, thiomorpholinyl, 1,1-dioxothiomorpholinyl, benzimidazolyl, benzothiazolyl, benzothienyl, benzoxazolyl, benzofuranyl, indolyl, indolinyl, isobenzofuranyl, isobenzothienyl, isoindolyl, isoindolinyl, isoquinolinyl, quinolinyl and the like. The heterocylyl radicals can carry one or more substituents, these being independently selected from alkenyl, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylcarbonyl, alkylcarbonylalkyl, alkylcarbonyloxy, alkylenedioxy, alkylsulphinyl, alkylsulphinylalkyl, alkylsulphonyl, alkylsulphonylalkyl, alkylthio, alkylthioalkyl, alkynyl, amino, aminoalkyl, aminocarbonyl, aminocarbonylalkyl, aryl, arylalkenyl, arylalkyloxy, arylalkyl, aryloxy, aryloxycarbonyl, aryloxycarbonylalkyl, arylsulphinyl, arylsulphinylalkyl, arylsulphonyl, arylsulphonylalkyl, arylthio, arylthioalkyl, carboxy, carboxyalkyl, cyano, cyanoalkyl, cycloalkyl, formyl, formylalkyl, halogen, haloalkoxy, haloalkyl, hydroxy, hydroxyalkyl, mercapto, nitro and the like.

The term "heteroaryl", alone or in combination, is a special case of heterocyclyl and describes a monocyclic, bicyclic or polycylic ring system, in which the or at least one ring is heteroaromatic.

The term "heterocyclylalkenyl", alone or in combination, describes a heterocyclyl group which is linked via an alkenyl group. Representative, but not limitative, examples of heterocyclylalkenyl are 2-pyrido-3-ylethenyl, 3-quinoline-3-ylpropen-2-yl, 5-pyrido-4-ylpentylen-4-yl and the like.

The term "heterocyclylalkoxy", alone or in combination, describes a heterocyclyl group which is linked via an alkoxy group. Representative, but not limitative, examples of heterocyclylalkoxy are 2-pyrido-3-ylethoxy, 3-quinoline-3-ylpropoxy, 5-pyrido-4-ylpentyloxy and the like.

The term "heterocyclylalkyl", alone or in combination, describes a heterocyclyl group which is linked via an alkyl group as defined. Representative, but not limitative, examples of heterocyclylalkyl are 2-pyrido-3-ylmethyl, 2-pyrimidine-2-ylpropyl and the like.

The term "heterocyclyloxy", alone or in combination, describes a heterocyclyl group which is linked via an oxygen bridge. Representative, but not limitative, examples of heterocyclyloxy are pyrido-3-yloxy, quinoline-3-yloxy and the like.

The terms "hydroxy" or "hydroxyl", alone or in combination, describe a -OH group.

The term "hydroxyalkyl", alone or in combination, describes an alkyl group in which at least one hydrogen atom is replaced by a hydroxyl group. Representative, but not limitative, examples of hydroxyalkyl are hydroxymethyl, 2-hydroxyethyl, 3-hydroxypropyl, 2-ethyl-4-hydroxyheptyl and the like.

The term "nitro", alone or in combination, describes a $-NO_2-$ group.

The term "oxo", alone or in combination, describes a =O- group.

The term "oxy", alone or in combination, describes a -O- group.

The terms "mercapto" and "thiol" describe a –SH- group.

The terms "thio", "sulphinyl" and "sulphonyl" describe a $-S(O)_n-$ group with n= 0,1 and 2.

The compounds defined at the outset of Formula I can be present in free form, as pharmaceutically applicable acid addition salts, as pharmaceutically applicable salts of acid compounds of Formula I with bases, as pharmaceutically applicable esters of hydroxy or carboxy group-containing compounds of Formula I and as hydrates or

solvates thereof. The term "pharmaceutically applicable salts" refers to salts which do not reduce the biological effect and properties of the free bases and which are not biologically or otherwise undesirable.

The acid addition salts are formed from the free bases using inorganic acids, such as hydrochloric acid, hydrobromic acid, sulphuric acid, nitric acid, phosphoric acid and the like., preferably hydrochloric acid or hydrobromic acid, or using organic acids, such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, tartaric acid, salicylic acid, citric acid, benzoic acid, mandelic acid, methanesulphonic acid, p-toluenesulphonic acid and the like.

Compounds of Formula I which contain acid groups can form salts with inorganic bases or with organic bases. Preferred salts with inorganic bases are, but not exclusively, sodium, potassium, lithium, ammonium, calcium, magnesium salts and the like. Preferred salts with organic bases are, but not exclusively, salts with primary, secondary and tertiary, optionally substituted amines including all naturally occurring substituted amines, with cyclic amines and with basic ion-exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, lysine, arginine, N-ethylpiperidine, piperidine, polyamine resins and the like. Compounds of Formula I which contain an acid group can also be present as zwitterions.

Pharmaceutically applicable esters of hydroxy or carboxy group-containing compounds of Formula I are also mentioned at the outset. "Pharmaceutically applicable esters" means that in compounds of Formula I corresponding functional groups are derivated to ester groups in such a way that they are transformed back to their active form again in vivo. On the one hand COOH groups can be esterified. Examples of suitable esters of this type are alkyl and aralkylesters. Preferred esters of this type are methyl, ethyl, propyl, butyl and benzylesters and (R/S)-1-[(isopropoxycarbonyl)oxy]ethyl esters. Ethyl esters and the isomeric butylesters are particularly preferred. On the other hand OH-groups can be esterified. Examples of such compounds contain physiologically

acceptable and metabolically labile ester groups, such as methoxymethyl esters, methylthiomethyl esters, pivaloyloxymethyl esters and similar ester groups.

Compounds of Formula I were examined in the following test for their affinity to the NPFF receptors:

Hamster cells suitable for neuropeptide FF receptor-binding studies (Chinese Hamster Ovary cells, CHOSP10) which in each case produce the NPFF1 or NPFF2 receptor, were multiplied in standard cell-culture conditions. The cell-culture medium was sucked out and 5 ml of buffer A (5 mM Tris pH=7.4, 1 mM $MgCl_2$) added per 17cm Petri dish. The cells were scraped off the cell-culture plate and transferred into a 50 ml Falcon vessel. The cells were then centrifuged for 5 minutes at 450 g, resuspended in buffer A once again and mixed for 30 seconds on a Polytron vortex. After centrifugation at 30,000 g for 20 minutes the supernatant was discarded and the membrane pellet taken up in 500 µl buffer C (75 mM Tris pH=7.4, 25 mM $MgCl_2$, 250 mM sucrose, 0.1 mM PMSF, 0.1 mM phenanthroline). The membrane-buffer mixture was then divided into aliquots and deep-frozen. The protein content of an aliquot was determined by the Lowry method.

The binding test was carried out in a final volume of 250 µl. 100 µl membrane-buffer mixture corresponding to 35 µg protein content was mixed with 95 µl binding buffer (50 mM Tris pH 7.4, 60 mM NaCl, 0.1 % protease-free BSA, 0.01% NaN_3). After addition of 5 µl each of a concentration of test substance per measurement point, 0.2 nM ^{125}I-Tyr1-NPFF (NEN, NEX381) per measurement point was added in 50 µl. After 90 minutes' incubation at room temperature the samples were sucked out through a GF/C filter (Millipore (MAHFC1H60)) and the filter was washed with ice cold binding buffer with 3 times 300 µl (Packard Filtermate). After addition of 55 µl Microscint 40 (Packard 6013641) scintillation fluid the measurement points were quantified in the gamma counter (Packard, Top Count NXT).

Non-specific binding was ascertained in the presence of 1 µM unmarked neuropeptide FF. Specific binding is defined as the difference between total and non-specific binding.

IC_{50} values are defined as that concentration of the antagonist which displaces 50% of the ^{125}I-marked neuropeptide FF. This concentration is ascertained by linear regression analysis after logit/log-transformation of the binding values.

Preferred compounds according to the invention show, in the receptor binding study described above, IC_{50} values below 1000 nM, particularly preferred compounds show IC_{50} values below 100 nM, quite particularly preferred ones, below 50 nM.

The results of the representative compounds of Formula I measured in the biological test described above are summarized in Table 1 below.

Table 1: NPFF1 receptor binding

Compound	Binding NPFF-1 IC50 [□M]
N-(5-ethyl-5-methyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine	0.0002
N-(5,5-dimethyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine	0.002
N-(4-*tert*-butyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine	0.002
N-(5,5-dimethyl-6-phenyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine	0.002
N-(6-isopropyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine	0.004
N-(6,6-dimethyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine	0.004
N-(5,5,7-trimethyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-	0.004

guanidine	
N-(5-butyl-5,6,7,8-tetrahydro-4H-cycloheptathiazol-2-yl)-guanidine	0.005
N-(5-butyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine	0.005
N-(4-ethyl-4-methyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine	0.005
N-[6-(3,4-dimethoxyphenyl)-4,5,6,7-tetrahydro-benzothiazole-2-yl]-guanidine	0.005
N-(5-Methyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine	0.006
N-(6-phenyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine	0.006
N-(6-propyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine	0.007
N-(4-methyl-4-propyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine	0.007
N-(4-cyclohex-1-enyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine	0.008
N-(4-*sec*-butyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine	0.009
N-(4-isobutyl-4-methyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine	0.009
N-(6-*tert*-butyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine	0.010

As mentioned at the outset, the substances defined there, because of their capacity to block the neuropeptide FF receptors, are valuable in the treatment of pain, hypersensitivity to pain (hyperalgesia) and chronic, acute, long-lasting or temporary

pain, which pain be of operative, traumatic, or pathological origin. Above all they supplement the current treatment methods for chronic pain with the advantage of preventing undesirable opioid tolerance and/or opioid dependence. The compounds can also be used for the regulation of insulin secretion, food intake, memory functions, blood pressure, and electrolyte and energy balance and for the treatment of urinary incontinence.

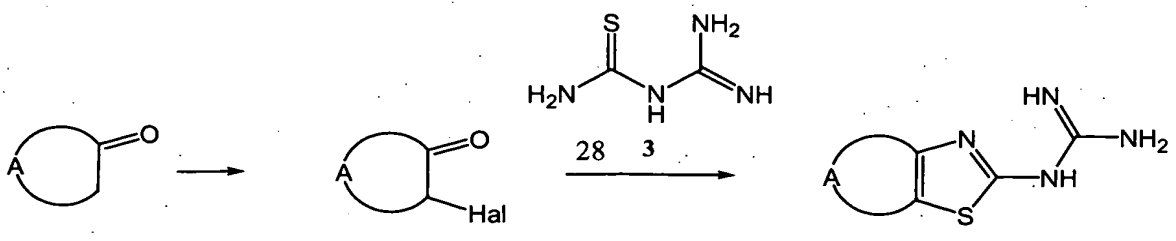
The substances defined at the outset can be transformed into suitable galenic dosage forms using methods which are generally known and familiar to every person skilled in the art. Such dosage forms are for example tablets, coated tablets, dragées, capsules, injection solutions etc. Suitable excipients and adjuvants are also generally known and familiar to every person skilled in the art for the preparation of such galenic dosage forms. In addition to one or more of the substances defined at the outset these dosage forms can also contain further pharmacologically active compounds.

The dosage of the substances defined at the outset or of the dosage forms containing them is to be matched by the doctor in attendance to the respective needs of the patient. In general a daily dose of 0.1-20 mg, preferably 0.5-5 mg of one of the substances defined at the outset per kg body weight of the patient should be appropriate.

The guanidine derivatives of general Formula I, and the corresponding starting and intermediate products, can be produced using methods known in organic synthesis and isolated and purified using known techniques such as precipitation, chromatography, crystallization, preparative *reversed-phase* HPLC, etc.. Stereoisomer mixtures which may be obtained, such as racemates, can be separated by generally customary methods, preferably by chiral-phase chromatography.

The preparation of the guanidine derivatives of general Formula I takes place according to Diagram 1 below:

Diagram 1



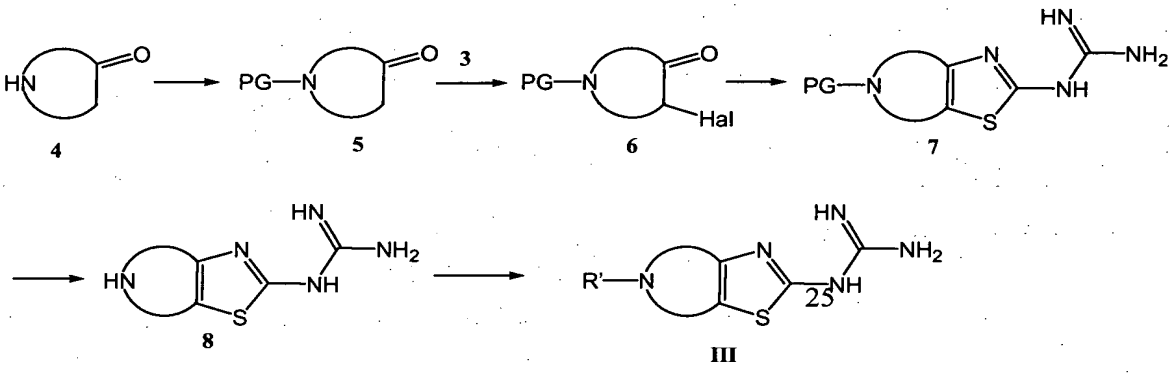
A compound of Formula **1**, in which the nitrogen atom which may be present in A is protected, is halogenated in α-position to form the carbonyl group, whereupon the obtained compound of Formula **2**, is subjected to a cyclocondensation with a thiourea derivate such as 2-imino-4-thiobiuret of Formula **3**, optionally the protective group located on the nitrogen atom which may be present is split off from the compound obtained, optionally this nitrogen atom is correspondingly substituted with an agent releasing a radical R' and optionally an obtained basic compound is converted into a pharmaceutically applicable acid addition salt, or an obtained compound, containing an acid group, into a pharmaceutically applicable salt with a base, or an obtained hydroxy or carboxy group-containing compound into a pharmaceutically applicable ester and optionally the obtained product is converted into a hydrate or solvate.

Because, in the novel compounds of Formula I, the chain A cannot contain a nitrogen atom, the above remarks concerning a N-protective group, its splitting-off and optional N-substitution of the end-product are irrelevant for the preparation of these novel compounds. Accordingly the novel products according to the invention can be produced by simply halogenating a compound of the above Formula **1** in α-position to form the carbonyl group, subjecting the obtained compound of the above Formula **2** to a cyclocondensation with 2-imino-4-thiobiuret of the above Formula **3** and optionally converting an obtained basic compound into a pharmaceutically applicable acid addition salt, or an obtained compound, containing an acid group, into a pharmaceutically applicable salt with a base, or an obtained hydroxy or carboxy group-containing compound into a pharmaceutically applicable ester and optionally the obtained product into a hydrate or solvate.

Typically the synthesis both of the guanidine derivatives of Formula I and of the corresponding intermediate products is carried out in solution using an organic solvent. The introduction and removal of protective groups takes place with typical methods known to a person skilled in the art (T.W. Greene & P.G.M. Wuts in Protective Groups in Organic Synthesis, Third Edition, John Wiley & Sons, 1999). Generally

cycloalkanones (**1**) can be halogenated with known methods in position α to form the carbonyl group. The following cyclocondensation of α-halo-oxo compounds (**2**) with a thiourea derivate, such as e.g. 2-imino-4-thiobiuret (**3**) takes place in known manner and leads to the desired guanidine derivatives of Formula I (J. Med. Chem. 1991, 34(3), 914-918; J. Med. Chem. 1994, 37(8), 1189-1199). Generally, heterocyclic oxo compounds (**1**) can be converted analogously to the corresponding target compounds of Formula I. It is to be borne in mind that an -NH-group present in A of the starting product (see Formula **4** below) is to be provided with a common protective group (PG), see Diagram 2 below:

Diagram 2



The required cyclic azaketones of Formula **4** are partly known from the literature (Yokoo et al., Bull. Chem. Soc. Japan 1959, 29, 631; Griss et al., DE 2206385, published 10th February 1972) or can be produced analogously to the precursor stage for Example N-07.

The halogenation of **5** and cyclocondensation of **6** with 2-imino-4-thiobiuret (**3**) to the correspondingly N-protected bicyclic guanidinothiazole **7** takes place under known conditions. After splitting-off of the protective group, which leads to **8**, the R'-radicals defined at the outset are converted under known conditions by means of the corresponding R'-releasing reagents in each case, such as e.g. alkylhalides, carboxylic acid halides or anhydrides, or also carboxylic acids in the presence of coupling reagents and with bases as auxiliary reagent, chloroformates, sulphonyl halides, isocyanates, isothiocyanates and the like to the corresponding compound of Formula III.

Suitable organic solvents are those which behave inertly under the chosen reaction conditions. These are preferably ethers, such as diethyl ether, dioxan, tetrahydrofuran or glycoldimethylether; or alcohols, such as for example methanol, ethanol, propanol, isopropanol, butanol, isobutanol or *tert*-butanol; or hydrocarbons, such as benzene, toluene, xylene, hexane, cyclohexane or petroleum fractions; or halogenated hydrocarbons, such as dichloromethane, trichloromethane, tetrachloromethane, dichloroethylene, trichloroethylene or chlorobenzene; or also ethyl acetate, triethylamine, pyridine, dimethylsulphoxide, dimethylformamide, hexamethylphosphoramide, acetonitrile, acetone or nitromethane. Mixtures of the solvents mentioned can also be used.

Bases which can be used for the described processes, are generally inorganic or organic bases. Preferred are alkali hydroxides, for example sodium or potassium hydroxide, alkaline-earth metal hydroxides, for example barium hydroxide, alkali carbonates such as sodium carbonate or potassium carbonate, alkaline-earth metal carbonates, such as calcium carbonate, or alkali or alkaline-earth metal alkoxides such as sodium or potassium methoxide, sodium or potassium methoxide or potassium-*tert*-butoxide, or organic amines, e.g. trialkyl-(C_1-C_6)-amines, such as triethylamine, or heterocyclic amines, such as 1,4-diazabicyclo[2.2.2]octane (DABCO), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), pyridine, 4-dimethylaminopyridine, N-methyl-piperidine or N-methylmorpholine. It is also possible to use alkali metals, such as sodium, or its hydrides, such as sodium hydride. The bases mentioned can, where expedient, be used as an acid-binding auxiliary.

Dehydrating reagents, for example carbodiimides, such as diisopropylcarbodiimide, dicyclohexylcarbodiimide or N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide-hydrochloride, or carbonyl compounds, such as carbonyldiimidazole, or 1,2-oxazolium compounds, such as 2-ethyl-5-phenyl-isoxazolium-3-sulphonate, or also propane phosphonic acid anhydride or isobutyl chloroformate or benzotriazolyloxy-tris-(dimethylamino)phosphonium-hexafluorophosphate (BOP) or diphenylphosphoramidate or methanesulphonyl chloride, if expedient in the presence of

bases, such as triethylamine or N-ethylmorpholine or N-methylpiperidine or diisopropylethylamine, can serve as coupling reagents.

The examples below serve to explain the present invention, but in no way limit it. The products obtained are given in Tables 3 and 4 below.

Example C-01

rac. N-(6-isopropyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine

2-imino-4-thiobiuret (5 mmol) is added accompanied by stirring to a solution of 2-bromo-4-isopropyl-cyclohexanone (5 mmol) in ethanol (10 ml) and the reaction mixture is then refluxed for 16 hours. After evaporating-off of the solvent ethyl acetate is added to the residue and the precipitated-out product is isolated by filtering off: t_R 2.75 min (LC-1, one peak); ESI-MS (+/-): *m/z* 239.25 $[M+H]^+$ / 237.24 $[M-H]^-$.

2-bromo-4-isopropyl-cyclohexanone (starting product for Example C-01)

Bromine (5 mmol) is added dropwise at room temperature to a solution of 4-isopropyl-cyclohexanone (5 mmol) in diethyl ether (10 ml). When the addition is complete the reaction mixture is stirred for another 30 min. After the addition of saturated aqueous sodium sulphite solution (5 ml) extraction is carried out with diethyl ether, the combined organic phases are concentrated by evaporation after drying over sodium sulphate. The bromoketone obtained as crude product is reacted directly in the next step with 2-imino-4-thiobiuret without further purification.

Analogously to the preparation of Example C-01, the compounds according to Examples C-02 to C-73 in Table 3 are prepared starting from the corresponding α-bromo- or α-chloroketones.

The bromination of the ketones used in Examples C-02 to C-17 takes place in a manner similar to that described above for the preparation of 2-bromo-4-isopropyl-cyclohexanone. The α-bromoketones are generally reacted as crude products without further characterization.

3-butylcyclohexanone (precursor-product for Example C-05)

A solution of copper iodide (6.3 mmol) in dimethyl sulphide (12 ml) is cooled to 50°C. A solution of butyl lithium (6.2 mmol) is added dropwise accompanied by stirring and stirred for a further 5 to 15 mins. The reaction mixture is cooled to -78°C and then a solution precooled to -78°C of cyclohex-2-enone (6 mmol), dissolved in dimethyl sulphide (1 ml), is slowly added dropwise. After stirring for one hour at -78°C the mixture is quenched with saturated aqueous ammonium chloride solution. The reaction mixture which has been heated to room temperature is extracted with diethyl ether. The combined ether phases are washed with saturated aqueous ammonium chloride solution and dried over sodium sulphate. After evaporating-off of the solvent the residue obtained is taken up in hexane, the solution is filtered and concentrated by evaporation. After chromatography of the residue on silica gel with ethyl acetate/ hexane 1:4 pure 3-butylcyclohexanone is obtained (Tetrahedron 1989, 45 (2), 425-434).

2-bromo-5-butyl-cyclohexanone (starting product for Example C-05)

The bromination of 3-butylcyclohexanone takes place in a manner similar to that described above for the preparation of 2-bromo-4-isopropyl-cyclohexanone. The title compound is reacted as a crude product without further characterization.

2-*tert*-butyl-6-chlorocyclohexanone (starting product for Example C-07)

N-butyl lithium is added dropwise to a solution, cooled to 0°C, of diisopropylamine (5.5 mmol) in dry tetrahydrofuran. After the addition is complete the mixture is cooled to -78°C, and a solution of 2-*tert*-butylcyclohexanone (5 mmol) in dry tetrahydrofuran (50 ml) is introduced, followed by the addition of p-toluenesulphonyl chloride (5 mmol), also dissolved in dry tetrahydrofuran (50 ml). The reaction mixture is heated to room temperature and after stirring for 30 mins over silica gel filtered with ether as eluant. After concentration by evaporation in a vacuum 2-*tert*-butyl-6-chlorcyclohexanone (760 mg) is obtained in a yield of 81% (Tet. Lett. 1999, 40(12), 2231-2234).

4,4-dimethylcyclohexanone (precursor-product for Example C-11)

A solution of 4,4-dimethyl-cyclohex-2-enone (3 mmol) in ethyl acetate is hydrogenated overnight at room temperature using Pd/C (0.05 mmol) with hydrogen under normal pressure. Filtration over celite and then concentration by evaporation produces 4,4-

dimethyl-cyclohexanone (355 mg) in a yield of 94% (J. Org. Chem. 2001, 66 (3), 733-738).

2-bromo-4,4-dimethylcyclohexanone (starting product for Example C-11)

The bromination of 4,4-dimethylcyclohexanone takes place in a manner similar to that described above for the preparation of 2-bromo-4-isopropyl-cyclohexanone. The title compound is reacted as a crude product without further characterization.

2-*sec*-butyl-6-chloro-cyclohexanone (starting product for Example C-18)

The chlorination of 2-*sec*-butylcyclohexanone takes place in a manner similar to that described above for the preparation of 2-*tert*-butyl-6-chloro-cyclohexanone. The title compound is reacted as a crude product without further characterization.

3-chloro-bicyclohexyl-1'-en-2-one (starting product for Example C-19)

The chlorination of 2-(1-cyclohexenyl)cyclohexanone takes place in a manner similar to that described above for the preparation of 2-*tert*-butyl-6-chloro-cyclohexanone. The title compound is reacted as a crude product without further characterization.

2-benzyl-6-chloro-cyclohexanone (starting product for Example C-20)

The chlorination of 2-benzylcyclohexanone takes place in a manner similar to that described above for the preparation of 2-*tert*-butyl-6-chloro-cyclohexanone. The title compound is reacted as a crude product without further characterization.

2-allyl-6-chloro-cyclohexanone (starting product for Example C-21)

The chlorination of 2-allylcyclohexanone takes place in a manner similar to that described above for the preparation of 2-*tert*-butyl-6-chloro-cyclohexanone. The title compound is reacted as a crude product without further characterization.

2-chloro-6-phenyl-cyclohexanone (starting product for Example C-22)

The chlorination of 2-phenylcyclohexanone takes place in a manner similar to that described above for the preparation of 2-*tert*-butyl-6-chloro-cyclohexanone. The title compound is reacted as a crude product without further characterization.

Ethyl (3-chloro-2-oxo-cyclohexyl)-acetate (starting product for Example C-23)
The chlorination of ethyl (2-oxo-cyclohexyl)-acetate takes place in a manner similar to that described above for the preparation of 2-*tert*-butyl-6-chloro-cyclohexanone. The title compound is reacted as a crude product without further characterization.

3-(3-chloro-2-oxo-cyclohexyl)-propionitrile (starting product for Example C-24)
The chlorination of 2-oxo-1-cyclohexanepropionitrile takes place in a manner similar to that described above for the preparation of 2-*tert*-butyl-6-chloro-cyclohexanone. The title compound is reacted as a crude product without further characterization.

2-chloro-6-methyl-cyclohexanone (starting product for Example C-25)
The chlorination of 2-methylcyclohexanone takes place in a manner similar to that described above for the preparation of 2-*tert*-butyl-6-chloro-cyclohexanone. The title compound is reacted as a crude product without further characterization.

2,2-dimethyl-cyclohexanone (precursor-product for Example C-26)
A suspension of potassium hydride (5.5 mmol) and 2-methylcyclohexanone (5 mmol) in dry tetrahydrofuran (10 ml) is stirred for 30 mins at room temperature. Triethylborane (6.25 mmol) is slowly added dropwise and the mixture is stirred for 16 hours at room temperature. After addition of methyl iodide stirring is continued for another 8 hours, the reaction is then quenched with saturated aqueous ammonium chloride solution and twice extracted with diethyl ether. The combined organic phases are dried over sodium sulphate and concentrated to dryness in a vacuum and produce the title compound, which can be reacted without [without] purification (*JACS* **1985**, 107, 19, 5391-5396).

6-bromo-2,2-dimethyl-cyclohexanone (starting product for Example C-26)
The bromination of 2,2-dimethyl-cyclohexanone takes place in a manner similar to that described above for the preparation of 2-bromo-4-isopropyl-cyclohexanone. The title compound is reacted as a crude product without further characterization.

2-ethyl-2-methyl-cyclohexanone (precursor-product for Example C-27)

The alkylation of 2-methylcyclohexanone with ethyl iodide takes place in a manner similar to that described above for the preparation of 2,2-dimethyl-cyclohexanone.

6-bromo-2-ethyl-2-methyl-cyclohexanone (starting product for Example C-27)

The bromination of 2-ethyl-2-methyl-cyclohexanone takes place in a manner similar to that described above for the preparation of 2-bromo-4-isopropyl-cyclohexanone. The title compound is reacted as a crude product without further characterization.

2-isobutyl-2-methyl-cyclohexanone (precursor-product for Example C-28)
The alkylation of 2-methylcyclohexanone with 1-iodo-2-methyl-propane takes place in a manner similar to that described above for the preparation of 2,2-dimethyl-cyclohexanone.

6-bromo-2-isobutyl-2-methyl-cyclohexanone (starting product for Example C-28)
The bromination of 2-isobutyl-2-methyl-cyclohexanone takes place in a manner similar to that described above for the preparation of 2-bromo-4-isopropyl-cyclohexanone. The title compound is reacted as a crude product without further characterization.

2-methyl-2-propyl-cyclohexanone (precursor-product for Example C-29)
The alkylation of 2-methylcyclohexanone with 1-iodopropane takes place in a manner similar to that described above for the preparation of 2,2-dimethyl-cyclohexanone.

6-bromo-2-methyl-2-propyl-cyclohexanone (starting product for Example C-29)

The bromination of 2-methyl-2-propyl-cyclohexanone takes place in a manner similar to that described above for the preparation of 2-bromo-4-isopropyl-cyclohexanone. The title compound is reacted as a crude product without further characterization.

Example C-30
2-guanidino-4,5,6,7-tetrahydro-benzothiazole-4-carboxylic acid ethyl ester

Analogously to the preparation of Example C-01, 3-bromo-2-oxo-cyclohexane carboxylic acid ethyl ester is reacted with 2-imino-4-thiobiuret to produce the title compound.

3-bromo-2-oxo-cyclohexane carboxylic acid ethyl ester (starting product for Example C-30)

The bromination of 2-oxo-cyclohexane carboxylic acid ethyl ester takes place in a manner similar to that described above for the preparation of 2-bromo-4-isopropyl-cyclohexanone. The title compound is reacted as a crude product without further characterization.

Guanidino-4,5,6,7-tetrahydro-benzothiazole-4-carboxylic acid

A suspension of 2-guanidino-4,5,6,7-tetrahydro-benzothiazole-4-carboxylic acid ethyl ester (5 mmol) and sodium hydroxide (20 mmol) in methanol/ water (4:1, 10 ml) is stirred overnight at room temperature. The pH is set at 5 by adding 25% hydrochloric acid and the precipitated product is filtered off. In this way the title compound is obtained (671 mg) in a yield of 56%: t_R 0.64 min (LC-1); ESI-MS (+/-): *m/z* 241.49 $[M+H]^+$ / 239.37 $[M-H]^-$.

Example C-31

2-guanidino-4,5,6,7-tetrahydro-benzothiazole-4-carboxylic acid benzylamide and its formate

2-guanidino-4,5,6,7-tetrahydro-benzothiazole-4-carboxylic acid (0.1 mmol), diisopropylethylamine (0.2 mmol), O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium-hexafluorophosphate (0.1 mmol) and benzylamine (0.2 mmol) are dissolved in dimethylformamide (0.5 ml) and stirred overnight at room temperature. After removal of the solvent in a vacuum the residue is dispersed in ethyl acetate (1 ml) and 1M aqueous caustic soda solution (0.5 ml). The phases are separated, the organic phase is dried over sodium sulphate, the solvent is evaporated off and the pure title compound is obtained using preparative HPLC (Waters Prep LC equipped with a Waters 600 Controller, Waters 2767 Sample Manager, Waters 996 mass spectrometer and photodiode-array detector).

Analogously to Example C-31 the compounds of Examples C-32 to C-41 listed in Table 3 are produced by reaction of 2-guanidino-4,5,6,7-tetrahydro-benzothiazole-4-carboxylic acid with the corresponding amines in the presence of a coupling reagent such as O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium-hexafluorophosphate.

Example C-42

2-guanidino-4,5,6,7-tetrahydro-benzothiazole-6-carboxylic acid ethyl ester

Analogously to the preparation of Example C-01, 3-bromo-4-oxo-cyclohexane carboxylic acid ethyl ester is reacted with 2-imino-4-thiobiuret to form the title compound.

3-bromo-4-oxo-cyclohexane carboxylic acid ethyl ester (Starting product for Example C-42)

The bromination of 4-oxo-cyclohexane carboxylic acid ethyl ester takes place in a manner similar to that described above for the preparation of 2-bromo-4-isopropyl-cyclohexanone. The title compound is reacted as a crude product without further characterization.

2-guanidino-4,5,6,7-tetrahydro-benzothiazole-6-carboxylic acid

Analogously to the preparation of 2-guanidino-4,5,6,7-tetrahydro-benzothiazole-4-carboxylic acid, 2-guanidino-4,5,6,7-tetrahydro-benzothiazole-6-carboxylic acid ethyl ester is saponified to form the title compound: t_R 2.49 min (LC-1); ESI-MS (+/-): *m/z* 241.04 $[M+H]^+$ / 238.39 $[M-2H]^-$.

In a similar way to Example C-31 the compounds of Examples C-43 to C-46 listed in Table 3 are produced by reaction of 2-guanidino-4,5,6,7-tetrahydro-benzothiazole-4-carboxylic acid with the corresponding amines in the presence of a coupling reagent such as O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium-hexafluorophosphate.

Example C-47

N-(tetrahydro-benzothiazole-2-yl-4-spiro-cyclohexane)-guanidine and its formate

Analogously to the preparation of Example C-01, 2-bromo-spiro[5.5]undecan-1-one is reacted with 2-imino-4-thiobiuret to form the title compound.

2-bromo-spiro[5.5]undecan-1-one (Starting product for Example C-47)

The bromination of spiro[5.5]undecan-1-one takes place in a manner similar to that described above for the preparation of 2-bromo-4-isopropyl-cyclohexanone. The title compound is reacted as a crude product without further characterization.

Spiro[5.5]undecan-1-one (precursor-product for Example C-47)

Dibromopentane (5 mmol) is added to a solution of cyclohexanone (5 mmol) and potassium-*tert*-butanolate (10 mmol) in toluene (7.5 ml) and the reaction mixture is refluxed for 48 hours. After cooling to room temperature 25% hydrochloric acid is added and extraction is carried out with diethyl ether. The combined organic phases produce, after drying over sodium sulphate, removal of the solvent in a vacuum and chromatography of the residue using silica gel (ethyl acetate/ heptane, 1:5) pure spiro[5.5]undecan-1-one (*Tetrahedron* 1964, 20, 2553-2573): t_R 1.90 min.(LC-2); ESI-MS (+): *m/z* 167.27 $[M+H]^+$.

Example C-48

N-(6-phenyl-4,5,6,7-tetrahydro-benzothiazole-2-yl-4-spiro-cyclohexane)-guanidine and its hydrobromide salt

The title compound is produced starting from 4-phenyl-spiro[5.5]undecan-1-one instead of spiro[5.5]undecan-1-one in a similar way to N-(tetrahydro-benzothiazole-2-yl-4-spiro-cyclohexane)-guanidine.

4-phenyl-spiro[5.5]undecan-1-one (precursor-product for Example C-48)

The preparation of the title compound takes place in a manner similar to that described above for the preparation of spiro[5.5]undecan-1-one: t_R 1.92 min (LC-2); ESI-MS(+): *m/z* 243.36 $[M+H]^+$. ^1H NMR (ppm,$CDCl_3$): 7.3(5H); 3.25(1H); 2.8(1H); 2.35(1H); 2.2(2H); 1.95(3H); 1.75(2H); 1.65(2H); 1.4(4H); 1.15(1H).

4,4-diphenylcyclohexanone (precursor-product for Example C-49)

The preparation of 4,4-diphenylcyclohexanone takes place in a manner similar to that described above for the preparation of 4,4-dimethylcyclohexanone: t_R 3.68 min (LC-1); ESI-MS(-): *m/z* 249.00 $[M-H]^-$.

2-bromo-4,4-diphenylcyclohexanone (starting product for Example C-49)
The bromination of 4,4-diphenylcyclohexanone takes place in a manner similar to that described above for the preparation of 2-bromo-4-isopropyl-cyclohexanone. The title compound is reacted as a crude product without further characterization.

3-bromo-4-oxo-1-phenyl-cyclohexane carboxylic acid ethyl ester (starting product for Example C-50)
The bromination of 4-oxo-1-phenyl-cyclohexane carboxylic acid ethyl ester takes place in a manner similar to that described above for the preparation of 2-bromo-4-isopropyl-cyclohexanone. The title compound is reacted as a crude product without further characterization.

3-bromo-4-oxo-1-phenyl-cyclohexanecarbonitrile (starting product for Example C-51)
The bromination of 4-oxo-1-phenyl-cyclohexanecarbonitrile takes place in a manner similar to that described above for the preparation of 2-bromo-4-isopropyl-cyclohexanone. The title compound is reacted as a crude product without further characterization.

3-bromo-4-arylcyclohexanone (Starting product[s] for Examples C-52 to C-66)
The bromination of the 4-arylcyclohexanone derivatives (precursor stages for Examples C-52 to C-66) takes place in a manner similar to that described above for the preparation of 2-bromo-4-isopropyl-cyclohexanone. The title compound is reacted as a crude product without further characterization.

Preparation of the 4-arylcyclohexanone derivatives (precursor-products for Examples C-54 to C-66):

1,4-dioxaspiro[4.5]dec-7-en-8-yl-trifluormethane-sulphonic acid ester

1,4-dioxaspiro[4.5]decan-8-one (1 mmol), dissolved in tetrahydrofuran (2 ml), is added to a solution, cooled to
-78°C, of lithium-bis-(trimethylsilyl)-amide (1M in tetrahydrofuran, 1.1 mmol) in dry tetrahydrofuran. The mixture is stirred for another 1.5 hours at -78°C and then a solution of N-phenyl-trifluormethanesulphonimide (1.07 mmol) in tetrahydrofuran (2 ml) is added. Then the mixture is stirred overnight at room temperature and the solvent is then removed in a vacuum. After drying of the residue in a vacuum 1,4-dioxaspiro[4.5]dec-7-en-8-yl-trifluormethane-sulphonic acid ester is obtained, which is immediately reacted again without additional purification (*Tetrahedron* **1999**, 55, 14479-14490): ^{1}H NMR (ppm,$CDCl_3$): 5.65(1H); 4(4H); 2.55(2H); 2.4(2H); 1.9(2H).

4-(4-fluorophenyl)-cyclohexanone (precursor-product for Example C-54)

a) 8-(4-fluorophenyl)-1,4-dioxaspiro[4.5]dec-7-ene:

In an argon-charged flask, 2M sodium carbonate (4.8 mmol), 1,2-dimethoxyethane (8 ml), 4-fluorophenylboric acid (2.8 mmol), lithium chloride (6 mmol), 1,4-dioxaspiro[4.5]dec-7-en-8-yl-trifluormethane-sulphonic acid ester (2 mmol) and tetrakis(triphenyl-phosphine)palladium (0.1 mmol) are combined and stirred overnight at 80°C. The reaction mixture is concentrated in a vacuum and the residue is dispersed in dichloromethane/ 2M aqueous sodium carbonate solution. The aqueous phase is extracted with dichloromethane. The combined organic phases are then dried over sodium sulphate and the solvent is evaporated off in a vacuum. From the residue, after column chromatography using silica gel (ethyl acetate/ heptane 1:4), pure 8-(4-fluorophenyl)-1,4-dioxaspiro[4.5]dec-7-ene is isolated (*Synthesis* **1993**, 735-762): t_R 3.61 min (LC-1); ESI-MS(+): *m/z* 235.34 $[M+H]^+$. ^{1}H NMR (ppm,$CDCl_3$): 7.35(2H); 6.95(2H); 5.9(1H); 4.05(4H); 2.65(2H); 2.45(2H); 1.9(2H).

b) 8-(4-fluorophenyl)-1,4-dioxaspiro[4.5]decane:

8-(4-fluorophenyl)-1,4-dioxaspiro[4.5]dec-7-ene is hydrogenated using Pd/C with hydrogen. After filtering-off of the catalyst over celite and evaporating-off of the solvent, 8-(4-fluorophenyl)-1,4-dioxaspiro[4.5]decane is obtained in a quantitative yield: t_R 3.65 min (LC-1); ESI-MS(+): *m/z* 237.26 $[M+H]^+$.

c) 4-(4-fluorophenyl)-cyclohexanone:

8-(4-fluor-phenyl)-1,4-dioxaspiro[4.5]decane (2 mmol) is dissolved in dioxane (6.5 ml) and treated with 3 ml 50% aqueous sulphuric acid accompanied by stirring at room temperature for 5 hours. After dilution with water (12 ml) extraction is carried out twice with dichloromethane. The raw title compound is obtained from the combined organic phases after drying over sodium sulphate and evaporating-off of the solvent in a vacuum (*Tetrahedron* **1998**, 54, 15509-15524): t_R 3.44 min (LC-1); ESI-MS(+): *m/z* 193.29 $[M+H]^+$.

The preparation of the precursor-products for Examples C-55 to C-66 takes place in a manner similar to that described above for the preparation of 4-(4-fluorophenyl)-cyclohexanone.

4-o-tolyl-cyclohexanone (precursor-product for Example C-55)

^1H NMR (ppm,$CDCl_3$): 7.3 (2H); 7.1 (2H); 3.15 (1H); 2.45 (4H); 2.35 (3H); 2.1 (2H); 1.85 (2H); 1.65(2H); 1.4(4H); 1.15(1H).

4-(2-ethyl-phenyl)-cyclohexanone (precursor-product for Example C-56)

t_R 3.62 min (LC-1); ESI-MS (+): *m/z* 203.29 $[M+H]^+$.

4-(3,4-dimethoxyphenyl)-cyclohexanone (precursor-product for Example C-57)

t_R 3.43 min (LC-1); ESI-MS (+): *m/z* 235.28 $[M+H]^+$.

4-(4-cyanophenyl)-cyclohexanone (precursor-product for Example C-58)

t_R 1.92 min (LC-2); ESI-MS (+): *m/z* 200.33 $[M+H]^+$.

4-(3,5-bis-trifluormethylphenyl)-cyclohexanone (precursor-product for Example C-59)

t_R 2.46 min (LC-2); ESI-MS (+): *m/z* 311.29 $[M+H]^+$.

4-p-tolyl-cyclohexanone (precursor-product for Example C-60)

t_R 2.11 min (LC-2); ESI-MS (+): *m/z* 189.32 $[M+H]^+$.

4-m-tolyl-cyclohexanone (precursor-product for Example C-61)
t_R 2.12 min (LC-2); ESI-MS (+): *m/z* 189.32 $[M+H]^+$.

4-(3-methoxy-phenyl)-cyclohexanone (precursor-product for Example C-62)
t_R 2.08 min (LC-2); ESI-MS (+): *m/z* 205.35 $[M+H]^+$.

4-(4-chloro-phenyl)-cyclohexanone (precursor-product for Example C-63)
t_R 2.26 min (LC-2); ESI-MS (+): *m/z* 209.23 $[M+H]^+$.

4-(3-fluorophenyl)-cyclohexanone (precursor-product for Example C-64)
t_R 2.11 min (LC-2); ESI-MS (+): *m/z* 193.26 $[M+H]^+$.

4-thiophene-2-yl-cyclohexanone (precursor-product for Example C-65)
t_R 2.05 min (LC-2); ESI-MS (+): *m/z* 219.29 $[M+H]^+$.

4-benzo[1,3]dioxol-5-yl-cyclohexanone (precursor-product for Example C-66)
t_R 2.05 min (LC-2); ESI-MS (+): *m/z* 181.23 $[M+H]^+$.

2-bromo-5,5-dimethyl-cyclohexanone (starting product for Example C-67);
2-bromo-5-ethyl-5-methyl-cyclohexanone (starting product for Example C-68) and
2-bromo-5-methyl-5-phenyl-cyclohexanone (starting product for Example C-69)
The bromination of 3,3-dimethyl-cyclohexanone, 3-ethyl-3-methyl-cyclohexanone, and 3-methyl-3-phenyl-cyclohexanone respectively (precursor stages of Examples C-67 to C-69) takes place in a manner similar to that described above for the preparation of 2-bromo-4-isopropyl-cyclohexanone. The title compounds are reacted as crude products without further characterization.

2-bromo-5,5-dimethyl-4-phenyl-cyclohexanone (starting product for Example C-70)
The bromination of 3,3-dimethyl-4-phenyl-cyclohexanone takes place in a manner similar to that described above for the preparation of 2-bromo-4-isopropyl-cyclohexanone. The title compound is reacted as a crude product without further characterization.

3,3-dimethyl-4-phenyl-cyclohexanone (precursor stage of Example C-70)
Lithium chloride (0.6 mmol) and copper iodide (0.3 mmol) are introduced first under argon in dry tetrahydrofuran (18 ml). At 0°C 3-methyl-4-phenylcyclohex-2-enone (3 mmol) is added and stirring continues for another 10 min at this temperature. Then a solution of methylmagnesium bromide (3.6 mmol) is slowly added dropwise and the reaction mixture is maintained at 0°C for 3 hours accompanied by stirring. The reaction is stopped by adding saturated aqueous ammonium chloride solution. The mixture is extracted with diethyl ether. The title compound is obtained from the combined organic phases after drying over sodium sulphate and evaporating-off of the solvent in a vacuum (*J. Organom. Chem.* **1995**, 502, C5-C7): t_R 2.36 min (LC-2); ESI-MS (+): *m/z* 203.35 $[M+H]^+$.

2-bromo-3-methyl-cyclohexanone (starting product for Example C-71)
A solution of N-bromosuccinimide (0.48 mmol) and sodium acetate (0.04 mmol) in THF/ water (1:1, 5.2 ml) is cooled to 0°C and trimethyl-(3-methyl-cyclohex-1-enyloxy)-silane (0.4 mmol, 80% pure) is added dropwise. The reaction mixture is heated to room temperature and stirring is continued overnight. After addition of water extraction is carried out with ethyl acetate. The title compound is obtained from the combined organic phases after drying over sodium sulphate and evaporating-off of the solvent in a vacuum (*JOC* **1997**, 62, 19, 6692-6696).

Trimethyl-(3-methyl-cyclohex-1-enyloxy)-silane (precursor-product for Example C-71)
Lithium chloride (2 mmol) and copper iodide (1 mmol) are introduced first under argon in tetrahydrofuran (5.6 ml) and cooled to -78°C. Cyclohex-2-enone (1 mmol) and trimethylsilyl chloride (1.1 mmol) are added and the solution is stirred for another 10 min. Then a solution of methylmagnesium bromide (1.2 mmol) is slowly added dropwise. After stirring for 3 hours at -78°C saturated aqueous ammonium chloride solution is added and extraction is carried out with ether. The combined organic phases are dried over sodium sulphate and the solvent is removed in a vacuum. The crude product obtained contains according to LC-MS 80% trimethyl-(3-methyl-cyclohex-1-enyloxy)-silane and 20% of the starting compound and is used in the subsequent

reaction without further purification (*J. Organom. Chem.* **1995**, 502, C5-C7): ^{1}H NMR (ppm, $CDCl_3$): 4.75(1H); 2.25(1H); 1.95(2H); 1.75(2H); 1.05(1H); 0.95 (3H); 0.2 (9H).

2-bromo-6-phenyl-cycloheptanone (starting product for Example C-72)

The bromination of 3-phenylcycloheptanone takes place in a manner similar to that described above for the preparation of 2-bromo-4-isopropyl-cyclohexanone. The title compound is reacted as a crude product without further characterization.

2-*tert*-butyl-6-chloro-4-phenyl-cyclohexanone (starting product for Example C-73)

The chlorination of 2-*tert*-butyl-4-phenyl-cyclohexanone takes place in a manner similar to that described above for the preparation of 2-*tert*-butyl-6-chloro-cyclohexanone. The title compound is reacted as a crude product without further characterization.

2-*tert*-butyl-4-phenyl-cyclohexanone (precursor stage for Example C-73)

a) Trimethyl-(4-phenyl-cyclohex-1-enyloxy)-silane:

sodium iodide (12.4 mmol) dissolved in acetonitrile (12.4 ml), is added dropwise at room temperature to a solution of 4-phenylcyclohexanone (10 mmol) in hexane (10 ml), followed by triethylamine (12.4 mmol) and trimethylchlorosilane (12.4 mmol). After stirring for two hours cold pentane and ice water are added. The aqueous phase is extracted with hexane. The combined organic phases are washed with ice water, dried over sodium sulphate and the solvent is removed in a vacuum. Trimethyl-(4-phenyl-cyclohex-1-enyloxy)-silane (1.8 g) is obtained in pure form in a yield of 73% (*Tetrahedron* 1987, 43, 9, 2075-2088): t_R 2.29 min (LC-2); ESI-MS (+): *m/z* 247.27 $[M+H]^+$.

b) 2-*tert*-butyl-4-phenyl-cyclohexanone:

Trimethyl-(4-phenyl-cyclohex-1-enyloxy)-silane (7.27 mmol) and *tert*-butyl chloride (7.85 mmol) are introduced first in dichloromethane under nitrogen and cooled to –45°C. A solution, also cooled to –45°C, of titanium tetrachloride (7.63 mmol) in dichloromethane (3.6 ml) is added, and stirring is continued for 3 hours at this temperature. The reaction mixture is diluted with dichloromethane and washed with ice water. The organic phase is dried over sodium sulphate and the solvent is removed in a

vacuum. Column chromatography (ethyl acetate/ heptane 1:4) of the residue produces the title compound (250 mg) in a yield of 15% (*Angew Chem Int Ed Engl* 1978, 17, 1, 48-49). ^{1}H NMR (ppm, $CDCl_3$): 7.35(5H); 3.15(1H); 2.55(1H); 2.4(3H); 2.25(1H); 2(1H); 1.8(1H); 1.05(9H).

Example N-01

2-guanidino-6,7-dihydro-4H-thiazolo[5,4-c]pyridine-5-carboxylic acid *tert*-butyl ester

Analogously to the preparation of Example C-01, 3-bromo-4-oxo-piperidine-1-carboxylic acid *tert*-butyl ester is reacted with 2-imino-4-thiobiuret to form the title compound. t_R 2.55 min (LC-1); ESI-MS (+): *m/z* 298.25 $[M+H]^+$.

3-bromo-4-oxo-piperidine-1-carboxylic acid *tert*-butyl ester (starting product for Example N-01)

The bromination of 4-oxo-piperidine-1-carboxylic acid *tert*-butyl ester takes place in a manner similar to that described above for the preparation of 2-bromo-4-isopropyl-cyclohexanone. The title compound is reacted as a crude product without further characterization.

N-(4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine-2-yl)-guanidine (splitting-off of the protective group from the product according to Example N-01, 2-guanidino-6,7-dihydro-4H-thiazolo[5,4-c]pyridine-5-carboxylic acid *tert*-butyl ester)

2-guanidino-6,7-dihydro-4H-thiazolo[5,4-c]pyridine-5-carboxylic acid *tert*-butyl ester (9.6 mmol) is suspended in a solution of ethanol (10 ml) and concentrated hydrochloric acid (3.8 ml) and stirred for 3 hours at room temperature. After filtration, the product is precipitated by adding ethyl acetate to the clear solution. The white precipitate is filtered off, washed with ethyl acetate and then dried in a vacuum. The title compound is obtained in pure form (1.63 g) as dihydrochloride salt in a yield of 62%: t_R 0.83 min (LC-1); ESI-MS (-): *m/z* 232.23 $[M-H]^-$.

Example N-02

N-(5-hexyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine-2-yl)-guanidine

1-bromohexane (0.11 mmol) is added to a suspension of N-(4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine-2-yl)-guanidine (0.1 mmol) and caesium carbonate (0.22 mmol) in dimethylformamide (0.3 ml) and the reaction mixture is stirred overnight at room temperature. After adding 2M caustic soda solution (1 ml) the mixture is extracted with ethyl acetate, the combined organic phases are dried over sodium sulphate and then concentrated by evaporation, the title compound being obtained in pure form.

Analogously to Example N-02 the compounds of Examples N-03 to N-10 listed in Table 4 are produced by reaction of N-(4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine-2-yl)-guanidine with the corresponding alkylhalides ("R'-reagents").

Example N-07

N-(5-benzyl-5,6,7,8-tetrahydro-4*H*-thiazolo[4,5-c]azepine-2-yl)-guanidine

Using an alternative method, analogously to the preparation of Example 1, 1-benzyl-4-bromo-azepan-3-one is reacted with 2-imino-4-thiobiuret to form the title compound.

1-benzyl-azepan-3-one (precursor-product of Example N-07)

a) 5-(benzyl-ethoxycarbonylmethyl-amino)-pentanoic acid:

N-benzylglycine ethyl ester (1.87 ml) and 5-bromovaleric acid ethyl ester (1.92 ml) are dissolved in dimethylformamide (100 ml) and stirred in the presence of potassium carbonate (1.66 g) for 2 days at room temperature. The reaction is quenched with saturated aqueous ammonium chloride solution, and extraction is carried out with ethyl acetate. After drying over sodium sulphate the combined organic phases are concentrated by evaporation. From the obtained residue, 5-(benzyl-ethoxycarbonylmethyl-amino)-pentanoic acid is isolated in a yield of 30% by chromatography using silica gel (ethyl acetate/heptane 1:5).

b) 1-benzyl-azepan-3-one:

A suspension of potassium *tert*-butylate (336 mg) in toluene (2.5 ml) is refluxed for 10 min. Then 5-(benzyl-ethoxycarbonylmethyl-amino)-pentanoic acid (695 mg) in toluene (1 ml) is slowly added to the suspension and when the addition is complete the mixture is refluxed for another 1.5 hours. After cooling to room temperature 25% hydrochloric

acid (1 ml) is added. The organic phase is separated off and washed with 25% hydrochloric acid (4x 1 ml). The combined hydrochloric-acid aqueous phases are then refluxed for 5 hours. After cooling to room temperature the solution is made alkaline (pH 11) with 2N caustic soda solution and extraction is carried out with ethyl acetate. The combined organic phases are concentrated by evaporation after drying over sodium sulphate. The obtained residue produces, after chromatography using silica gel (ethyl acetate/ heptane 1:5) the desired title compound (197 mg) in a yield of 45 % (*Bull. Chem. Soc. Jpn.* 1956, 29, 631-632; DE2206385).

1-benzyl-4-bromo-azepan-3-one (starting product for Example N-07)
The bromination of 1-benzyl-azepan-3-one takes place in a manner similar to that described above for the preparation of 2-bromo-4-isopropyl-cyclohexanone. The title compound is reacted as a crude product without further characterization.

Example N-11
N-(pentanoyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine-2-yl)-guanidine
Diisopropylethylamine (0.22 mmol) and then pentanoyl chloride (0.11 mmol) are added to a stirred suspension of N-(4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine-2-yl)-guanidine-dihydrochloride (0.1 mmol) in dimethylformamide (0.7 ml) and the reaction mixture is stirred for another 16 hours at room temperature. After the addition of 2M caustic soda solution (1 ml) extraction is carried out with ethyl acetate. The combined organic phases produce the pure title compound after drying over sodium sulphate and concentrating to dryness.

Analogously to Example N-11, the compounds of Examples N-13 to N-33 listed in Table 4 are produced by reaction of N-(4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine-2-yl)-guanidine with the corresponding acid chlorides ("R'-reagents").

Example N-12
N-(5-but-3-enoyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine-2-yl)-guanidine
Diisopropylethylamine (0.22 mmol), vinyl acetic acid (0.11 mmol) and benzotriazolyloxy-tris-(dimethylamino)phosphonium-hexafluorophosphate (0.11 mmol)

are added successively to a stirred suspension of N-(4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine-2-yl)-guanidine-dihydrochloride (0.1 mmol) in dimethylformamide (0.7 mL), and the reaction mixture is stirred for 16 hours at room temperature. After the addition of 2M caustic soda solution (1 ml) there is extraction with ethyl acetate. The combined organic phases produce the pure title compound after drying over sodium sulphate and concentrating to dryness.

Analogously to Example N-12 the compounds of Examples N-19 to N-21 listed in Table 4 are realized by reaction of N-(4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine-2-yl)-guanidine with the corresponding carboxylic acids ("R'-reagents") in the presence of benzotriazolyloxy-tris-(dimethylamino)phosphonium-hexafluorophosphate as coupling reagent.

Example N-22

2-guanidino-6,7-dihydro-4*H*-thiazolo[5,4-c]pyridine-5-carboxylic acid benzyl ester

Benzyl chloroformate is added to a stirred suspension of N-(4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine-2-yl)-guanidine (0.1 mmol) and diisopropylethylamine (0.22 mmol) in dimethylformamide (0.7 ml) and the mixture is stirred for another 3 hours at room temperature. After the addition of saturated aqueous sodium carbonate solution extraction is carried out with ethyl acetate; the combined organic phases produce the pure title compound after drying over sodium sulphate and complete evaporation of the solvent.

Analogously to Example N-22 the compound of Example N-23 listed in Table 4 is produced by reaction of N-(4, 5, 6, 7-tetrahydro-thiazolo[5,4-c]pyridine-2-yl)-guanidine with butyl chloroformate ("R'-reagent").

Example N-24

N-[5-(propane-2-sulphonyl)-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine-2-yl)]-guanidine

Propane-2-sulphonyl chloride is added to a stirred suspension of N-(4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine-2-yl)-guanidine (0.1 mmol) and diisopropylethylamine (0.22 mmol) in dimethylformamide (0.7 ml) and the mixture is stirred for another 16 hours at

room temperature. After the addition of 2M caustic soda solution (1 ml) extraction is carried out with ethyl acetate; the combined organic phases produce [from] the pure title compound after drying over sodium sulphate and complete evaporation of the solvent.

Analogously to Example N-24 the compounds of Examples N-25 and N-26 listed in Table 4 are produced by reaction of N-(4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine-2-yl)-guanidine with the corresponding sulphonyl chlorides ("R'-reagents").

Example N-27

2-guanidino-6,7-dihydro-4H-thiazolo[5,4-c]pyridine-5-carboxylic acid phenyl amide

Diisopropylethylamine (0.2 mmol) and, after 5 min, phenyl isocyanate (0.11 mmol) are added to a suspension of N-(4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine-2-yl)-guanidine dihydrochloride (0.1 mmol) in dimethylformamide (0.5 ml). The reaction mixture is stirred for another 3 hours at room temperature. Then saturated aqueous sodium carbonate solution is added and extraction is carried out with ethyl acetate. The pure title compound is obtained after drying of the combined organic phases over sodium sulphate and removal of the solvent in a vacuum.

Analogously to Example N-27 the compounds of Examples N-28 and N-29 listed in Table 4 are produced by reaction of N-(4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine-2-yl)-guanidine dihydrochloride with the "R'-reagents" *tert*-butyl isocyanate, and pentyl isocyanate respectively.

Example N-30

2-guanidino-6,7-dihydro-4*H*-thiazolo[5,4-c]pyridine-5-thiocarboxylic acid benzyl amide

Benzylamine (0.1 mmol), dissolved in dimethylformamide (0.3 ml), is added under argon to a solution of 1'-thiocarbonyldiimidazole (0.1 mmol) in dimethylformamide (0.5 ml). After stirring for 2.5 hours at room temperature a solution of N-(4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine-2-yl)-guanidine dihydrochloride (0.1 mmol) and diisopropylethylamine (0.2 mmol) in dimethylformamide are added successively to the reaction mixture. This is stirred for another 16 hours at room temperature and then

quenched with saturated aqueous sodium carbonate solution. There is extraction with ethyl acetate and the combined organic phases are dried over sodium sulphate. After removal of the solvent in a vacuum the pure title compound is obtained (*Bioog. Med. Chem. Lett.* 2002, 12, 337-340).

Analogously to Example N-30 the compounds of Examples N-31 to N-33 listed in Table 4 are produced by reaction of N-(4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine-2-yl)-guanidine dihydrochloride with the corresponding amines in the presence of 1'-thiocarbonyldiimidazole.

Preparative LC-MS

Preparative separations of mixtures of substances are carried out on a preparative LC-MS apparatus (Waters Prep LC-MS equipped with a Waters 600 Controller, Waters 2767 Sample Manager, Waters 996 mass spectrometer and photodiode-array detector). An Xterra Prep MS C18 column (5 µm particle size, length 50 mm, diameter 19 mm) is used, with a linear gradient of water/0.06% formic acid (A) and acetonitrile/0.06% formic acid (B) and a flow rate of 20 ml/min.

Analytical methods

The ^{1}H-NMR-spectra are measured on a Varian Oxford 300 spectrometer at 300 K; the chemical shift δ is given in ppm deep field shifted from the tetramethylsilane signal as reference, with the residual signals of deuterated dimethyl sulphoxide (δ(H) 2.49 ppm), deuterated chloroform (δ(H) 7.24 ppm) and deuterium oxide serving as internal standard.

Table 2

1H-NMR data of selected compounds of Formula I.

Example	Chemical shift in ppm (Integral)	Solvent
C-02	8 (4H); 2.65 (3H); 2.15 (1H); 1.85 (2H); 1.4 (1H); 1 (3H)	DMSO-d_6
C-05	6.8 (4H); 2.5 (4H); 2.05 (1H); 1.85 (1H); 1.65 (1H); 1.3 (6H), 0.95 (3H)	DMSO-d_6
C-06	6.8 (4H); 2.75 (1H); 2.45 (4H); 1.8 (2H); 1.45 (2H); 1.2 (6H), 0.95 (3H)	D_2O
C-09	8.1 (4H); 7.3 (4H); 7.2 (1H); 2.95 (2H); 2.75 (3H); 2 (3H)	DMSO-d_6
C-12	7 (4H); 2.75 (1H); 2.45 (1H); 2.25 (1H); 1.55 (1H); 1.15 (1H); 1.1 (3H); 1 (3H); 0.85 (3H)	DMSO-d_6
C-24	8.3 (4H); 7.4 (5H); 4.35 (2H); 4.25 (2H); 3.55 (2H); 2.9 (2H); 2.1 (2H)	DMSO-d_6
C-38	8.1 (1H); 7.65 (1H); 6.9 (4H); 3.5 (1H); 3.3 (1H); 1.95-1.5 (10H); 1.15 (5H)	DMSO-d_6
C-42	8.1 (4H); 4.1 (2H); 2.85 (3H); 2.65 (2H); 2.1 (1H); 1.85 (1H); 1.15 (3H)	DMSO-d_6
C-50	8.1 (4H); 7.3 (5H); 4.05 (2H); 3.45 (1H); 3.1 (1H); 2.65 (1H); 2.4 (3H); 1.05 (3H)	DMSO-d_6
C-54	8.1 (4H); 7.35 (2H); 7.1 (2H); 3 (2H); 2.7 (3H); 2 (2H)	DMSO-d_6
C-57	8.1 (4H); 6.85 (3H); 3.75 (3H); 3.7 (3H); 2.95 (2H); 2.7 (3H); 2 (2H)	DMSO-d_6
C-71	2.8 (1H); 2.5 (2H); 1.85 (2H); 1.6 (1H); 1.3 (1H); 1.15 (3H)	$CDCl_3$
N-07	8.3 (4H); 7.4 (5H); 4.35 (2H); 4.25 (2H); 3.55 (2H); 2.9 (2H); 2.05 (2H)	D_2O
N-08	6.8 (4H); 3.05 (2H); 3 (2H); 2.7 (3H); 2.5 (2H)	DMSO-d_6
N-13	6.8 (4H); 4.5 (2H); 3.75 (2H); 2.95 (1H); 2.6 (1H); 2.5 (1H); 1 (6H)	DMSO-d_6
N-22	7.3 (5H); 6.8 (4H); 5.1 (2H); 4.45 (2H); 3.7 (2H); 2.55 (2H)	DMSO-d_6
N-26	7 (4H); 4.2 (2H); 3.45 (2H); 2.9 (3H); 2.65 (2H)	DMSO-d_6
N-29	6.8 (4H); 6.55 (1H); 4.3 (2H); 3.6 (2H); 3 (2H); 2.5 (2H); 1.4 (2H); 1.25 (4H); 0.85 (3H)	DMSO-d_6
N-30	8.35 (1H); 7.25 (5H); 6.8 (4H); 4.85 (2H); 4.8 (2H); 4.1 (2H); 2.6 (2H)	DMSO-d_6

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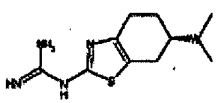
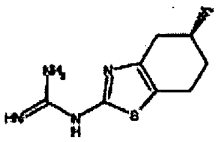
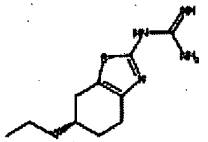
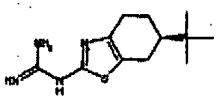
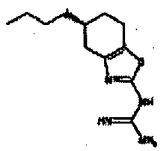
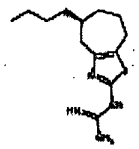
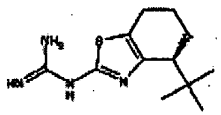
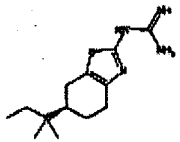
The compounds produced are analyzed by means of *reversed-phase* HPLC, on a Waters Alliance LC, equipped with a UV-detector and a MassLynx-NT mass spectrometer.

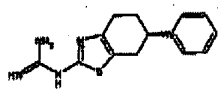
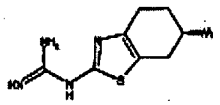
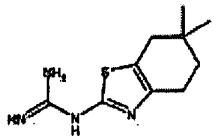
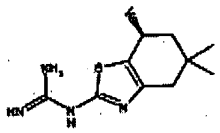
LC-1: GROM-SIL 120 ODS-4 HE HPLC column (particle size 3μm, column length 30 mm, diameter 2mm), with a linear gradient with water/0.06% formic acid (A) and acetonitrile/0.06% formic acid (B) of 5% to 95% B in 3 min. with a flow rate of 0.75 ml/min.

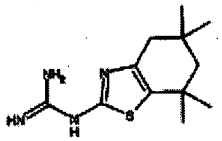
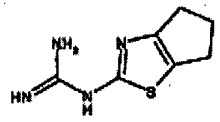
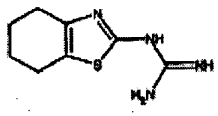
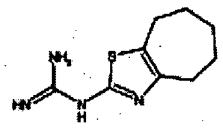
LC-2: XTerra MS C18 HPLC column (particle size 5μm, column length 50 mm, diameter 2.1 mm), with a linear gradient with water/0.06% formic acid (A) and acetonitrile/0.06% formic acid (B) of 5% to 95% B in 2.5 min. with a flow rate of 0.75 ml/min.

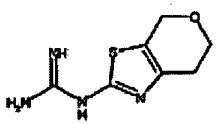
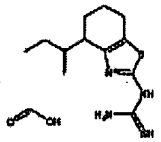
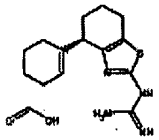
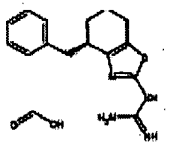
Table 3: Analytical data for Examples C-01 to C-73

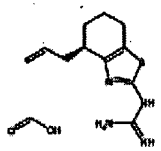
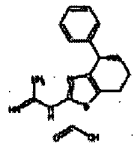
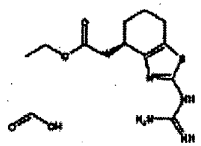
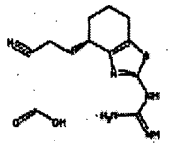
Example	Structure	Name	Starting product	Empirical formula Molecular weight	t_R [min] (HPLC method)	MS data *m/z* $[M+H]^+$/ $[M-H]^-$
C-01		N-(6-isopropyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine	4-isopropyl-cyclohexanone	C11H18N4S 238.4	2.75 (LC-1)	239.25/237.24
C-02		N-(5-methyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine	3-methyl-cyclohexanone	C9H14N4S 210.3	2.86 (LC-1)	211.25/209.26
C-03		N-(6-propyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine	4-n-propyl-cyclohexanone	C11H18N4S 238.4	2.79 (LC-1)	239.2/237.27
C-04		N-(6-tert-butyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine	4-*tert*-butyl-cyclohexanone	C12H20N4S 252.4	3.06 (LC-1)	253.28/251.36

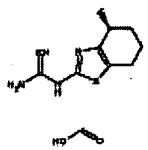
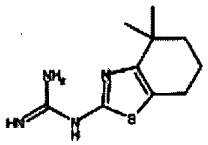
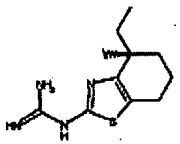
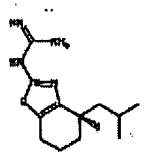
Example	Structure	Name	Starting product	Empirical formula Molecular weight	t_R [min] (HPLC method)	MS data *m/z* $[M+H]^+$/ $[M-H]^-$
C-05		N-(5-butyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine	3-butyl-cyclohexanone	C12H20N4S 252.4	3.19 (LC-1)	253.31/251.32
C-06		N-(5-butyl-5,6,7,8-tetrahydro-4H-cycloheptatthiazol-2-yl)-guanidine	3-butyl-cycloheptanone	C13H22N4S 266.4	3.2 (LC-1)	267.35/265.36
C-07		N-(4-*tert*-butyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine	2-*tert*-butyl-cyclohexanone	C12H20N4S 252.4	3.51 (LC-1)	253.37/251.45
C-08		N-[6-(1,1-dimethyl-propyl)-4,5,6,7-tetrahydro-benzothiazole-2-yl]-guanidine	4-*tert*-amyl-cyclohexanone	C13H22N4S 266.4	2.82 (LC-1)	267.24/265.36

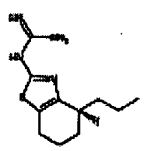
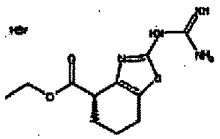
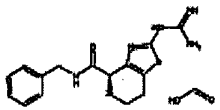
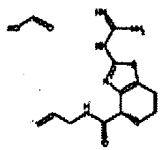
Example	Structure	Name	Starting product	Empirical formula Molecular weight	t_R [min] (HPLC method)	MS data *m/z* $[M+H]^+$/ $[M-H]^-$
C-09		N-(6-phenyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine	4-phenyl-cyclohexanone	C14H16N4S 272.4	2.74 (LC-1)	273.20/271.30
C-10		N-(6-methyl 4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine	4-methyl-cyclohexanone	C9H14N4S 210.3	2.7 (LC-1)	211.24/209.19
C-11		N-(6,6-dimethyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine	4,4--dimethyl-cyclohexanone	C10H16N4S 224.3	3.28 (LC-1)	225.36/223.37
C-12		N-(5,5,7-triimethyl--4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine	3,3,5-trimethyl-cyclohexanone	C11H18N4S 238.4	3.34 (LC-1)	239.33/237.36

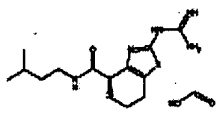
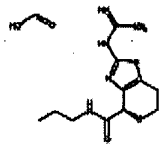
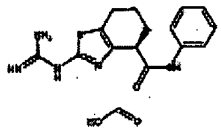
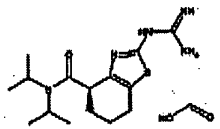
Example	Structure	Name	Starting product	Empirical formula Molecular weight	t_R [min] (HPLC method)	MS data *m/z* $[M+H]^+$/ $[M-H]^-$
C-13		N-(5,5,7,7-tetramethyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine	3,3,5,5-tetramethyl-cyclohexanone	C12H20N4S 252.4	2.73 (LC-1)	253.21/251.26
C-14		N-(5,6-dihydro-4H-cyclopenta-thiazol-2-yl)-guanidine	cyclopentanone	C7H10N4S 182.2	2.83 (LC-1)	183.31/181.32
C-15		N-(4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine	cyclohexanone	C8H12N4S 196.3	2.75 (LC-1)	197.22/195.34
C-16		N-(5,6,7,8-tetrahydro-4*H*-cycloheptathiazol-2-yl)-guanidine	cycloheptanone	C9H14N4S 210.3	2.89 (LC-1)	211.25/209.26

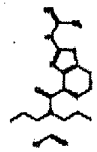
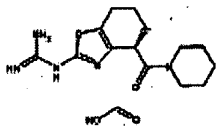
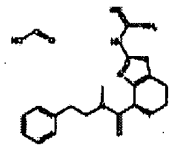
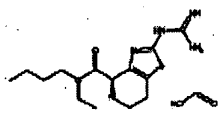
Example	Structure	Name	Starting product	Empirical formula Molecular weight	t_R [min] (HPLC method)	MS data *m/z* $[M+H]^+$/ $[M-H]^-$
C-17		N-(6,7-dihydro-4H-pyrano[4,3-d]thiazol-2-yl)-guanidine	tetrahydropyran-4-one	C7H10N4OS 198.2	1.76 (LC-1)	199.27/197.31
C-18		N-(4-*sec*- butyl-4,5,6,7-tetrahydro-benzothiazole 2-yl)-guanidine formate	2-*sec*-butylcyclo-hexanone	C13H22N4O2S 298.4	3.09 (LC-1)	253.28/251.36
C-19		N-(4-cyclohex-1-enyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)guanidine formate	2-(1-cyclo-hexenyl)cyclo-hexanone	C15H22N4O2S 322.4	3.13 (LC-1)	277.25/275.39
C-20		N-(4-benzyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)guanidine formate	2-benzyl-cyclohexanone	C16H20N4O2S 332.4	3.09 (LC-1)	287.25/285.27

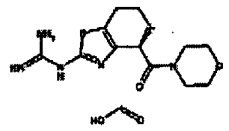
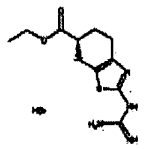
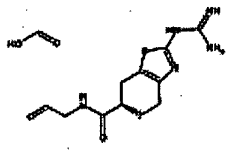
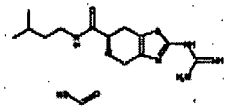
Example	Structure	Name	Starting product	Empirical formula Molecular weight	t_R [min] (HPLC method)	MS data *m/z* $[M+H]^+$/ $[M-H]^-$
C-21		N-(4-allyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine formate	2-allyl-cyclohexanone	C12H18N4O2S 282.3	2.99 (LC-1)	237.26/235.71
C-22		N-(4-phenyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine formate	2-phenyl-cyclohexanone	C15H18N4O2S 318.4	3.05 (LC-1)	273.66
C-23		(2-guanidino-4,5,6,7-tetra-hydro-benzothiazole-4-yl)-acetic acid ethyl ester formate	ethyl(2-oxo-cyclohexyl)-acetate	C13H20N4O4S 328.4	1.54 (LC-2)	283.08
C-24		N-[4-(2-cyano-ethyl)-4,5,6,7-tetrahydro-benzothiazole-2-yl]-guanidine formate	2-oxo-1-cyclohexane-propionitrile	C12H17N5O2S 295.3	2.81 (LC-1)	250.08

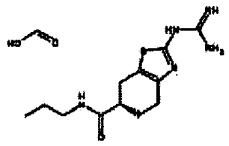
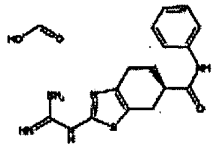
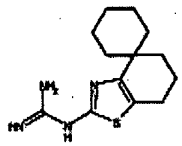
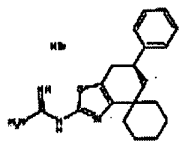
Example	Structure	Name	Starting product	Empirical formula Molecular weight	t_R [min] (HPLC method)	MS data *m/z* $[M+H]^+$/ $[M-H]^-$
C-25		N-(4-methyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine formate	2-methyl-cyclohexanone	C10H16N4O2S 256.3	2.87 (LC-1)	211.33
C-26		N-(4,4-dimethyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine	2,2-dimethyl-cyclohexanone	C10H16N4S 224.3	2.95 (LC-1)	225.92
C-27		N-(4-ethyl-4-methyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine	2-ethyl-2-methyl-cyclohexanone	C11H18N4S 238.3	2.99 (LC-1)	239.7
C-28		N-(4-isobutyl-4-methyl 4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine	2-isobutyl-2-methyl-cyclohexanone	C13H22N4S 266.4	3.11 (LC-1)	267

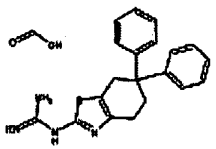
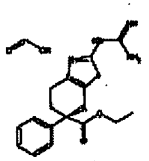
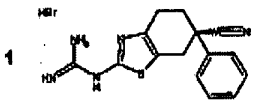
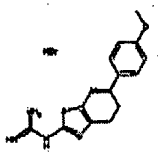
Example	Structure	Name	Starting product	Empirical formula Molecular weight	t_R [min] (HPLC method)	MS data *m/z* $[M+H]^+$/ $[M-H]^-$
C-29		N-(4-methyl—4-propyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine	2-methyl-2-propyl-cyclohexanone	C12H20N4S 252.4	3.07 (LC-1)	253.67
C-30		2-guanidino-4,5,6,7-tetrahydro-benzo-thiazol-4-carboxylic acid ethyl ester hydrobromide	2-oxo- cyclohexane carboxylic acid ethyl ester	C11H17BrN4O2S 349.2	1.54 (LC-2)	269.01/267.22
C-31		2-guanidino-4,5,6,7-tetra-hydro-benzothiazole-4-carboxylic acid benzylamide formate	2-guanidino-4,5,6,7-tetrahydro-benzothiazole-4-carboxylic acid	C17H21N5O3S 375.4	1.45 (LC-2)	330.26/328.16
C-32		2-guanidino-4,5,6,7-tetrahydro-benzothiazole-4-carboxylic acid allyl amide formate	2-guanidino-4,5,6,7- tetrahydro-benzothiazole-4-carboxylic acid	C13H19N5O3S 325.4	1.18 (LC-2)	280.18/278.18

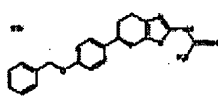
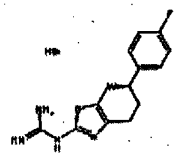
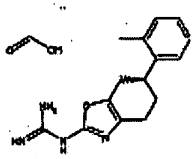
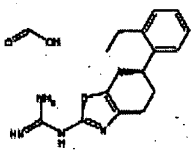
Example	Structure	Name	Starting product	Empirical formula Molecular weight	t_R [min] (HPLC method)	MS data *m/z* $[M+H]^+/[M-H]^-$
C-33		2-guanidino-4,5,6,7-tetrahydro-benzothiazole-4-carboxylic acid-(3-methyl-butyl)-amide formate	2-guanadino-4,5,6,7-tetrahydro-benzothiazole-4-carboxylic acid	C15H25N5O3S 355.5	1.43 (LC-2)	310.27/308.23
C-34		2-guanidino-4,5,6,7-tetrahydro-benzo-thiazol-4-carboxylic acid propylamide formate	2-guanidino- 4,5,6,7-tetrahydro-benzothiazole-4-carboxylic acid	C13H21N5O3S 327.4	1.25 (LC-2)	282.19/280.21
C-35		2-guanidino-4,5,6,7-tetra-hydro-benzothiazole-4-carboxylic acid phenylamide formate	2-guanidino-4,5,6,7-tetrahydro-benzothiazole-4-carboxylic acid	C16H19N5O3S 361.4	1.44 (LC-2)	316.19/314.15
C-36		2-guanidino-4,5,6,7-tetrahydro-benzothiazole-4-caboxylic acid diisopropylamide formate	2-guanidino-4,5,6,7-tetrahydro-benzothiazole-4-carboxylic acid	C16H27N5O3S 369.488	1.53 (LC-2)	324.15/n.a

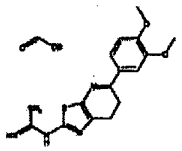
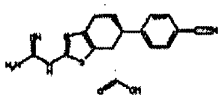
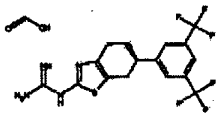
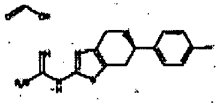
Example	Structure	Name	Starting product	Empirical formula Molecular weight	t_R [min] (HPLC method)	MS data *m/z* $[M+H]^+$/ $[M-H]^-$
C-37		2-guanidino-4,5,6,7-tetrahydro-benzothiazole-4-carboxylic acid-dipropylamide formate	2-guanidino-4,5,6,7-tetrahydro-benzothiazole-4-carboxylic acid	C16H27N5O3S 369.5	1.53 (LC-2)	324.28/322.24
C-38		N-[4-(piperidin-1-carbonyl)-4,5,6,7-tetrahydro-benzo-thiazol-2-yl]guanidine formate	2-guanidino- 4,5,6,7-tetrahydro-benzothiazole-4-carboxylic acid	C15H23N5O3S 353.4	1.37 (LC-2)	308.29/306.26
C-39		2-guanidino-4,5,6,7-tetrahydro-benzothiazole-4-carboxylic acid – methylphenethyl-amide formate	2-guanidino-4,5,6,7-tetrahydro-benzothiazole-4-carboxylic acid	C19H25N5O3S 403.5	1.55 (LC-2)	358.22/356.25
C-40		2-guanidino-4,5,6,7-tetrahydro-benzothiazole-4-caboxylic acid-butyl-ethyl-amide formate	2-guanidino-4,5,6,7-tetrahydro-benzothiazole-4-carboxylic acid	C16H27N5O3S 369.5	1.51 (LC-2)	324.28/322.24

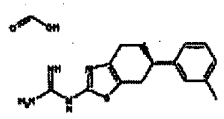
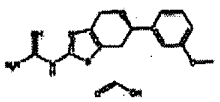
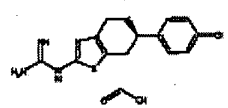
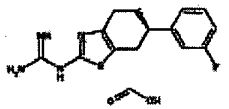
Example	Structure	Name	Starting product	Empirical formula Molecular weight	t_R [min] (HPLC method)	MS data *m/z* $[M+H]^+$/ $[M-H]^-$
C-41		N-[4-(morpholine-4-carbonyl)-4,5,6,7-tetrahydro-benzothiazole-2-yl-guanidine formate	2-guanidino-4,5,6,7-tetrahydro-benzothiazole-4-carboxylic acid	C14H21N5O4S 355.4	1.21 (LC-2)	310.20/308.23
C-42		2-guanidino-4,5,6,7-tetrahydro-benzo-thiazol-6-carboxylic acid-ethyl ester hydrobromide	4-oxo-cyclohexane carboxylic acid ethyl ester	C11H17BrN4O2S 349.2	2.76 (LC-1)	270.59/266.22
C-43		2-guanidino-4,5,6,7-tetrahydro-benzothiazole-6-carboxylic acid – allyl amide formate	2-guanidino-4,5,6,7-tetrahydro-benzothiazole-6-carboxylic acid	C13H19N5O3S 325.4	1.2 (LC-2)	280.15/278.18
C-44		2-guanidino-4,5,6,7-tetrahydro-benzothiazole-6-caboxylic acid-(3-methyl-butyl)-amide formate	2-guanidino-4,5,6,7-tetrahydro-benzothiazole-6-carboxylic acid	C15H25N5O3S 355.5	1.46 (LC-2)	310.33/308.29

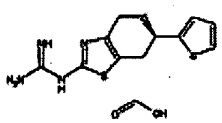
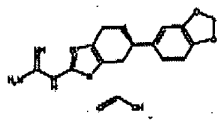
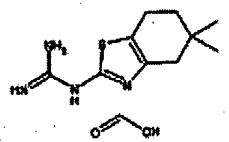
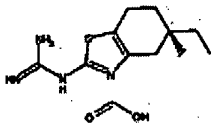
Example	Structure	Name	Starting product	Empirical formula Molecular weight	t_R [min] (HPLC method)	MS data *m/z* $[M+H]^+$/ $[M-H]^-$
C-45		2-guanidino-4,5,6,7-tetrahydro-benzothiazole-6-carboxylic acid-propylamide formate	2-guanidino-4,5,6,7-tetrahydro-benzothiazole-6-carboxylic acid	C13H21N5O3S 327.4	1.27 (LC-2)	282.12
C-46		2-guanidino-4,5,6,7-tetrahydro-benzo-thiazol-6-carboxylic acid-phenylamide formate	2-guanidino-4,5,6,7-tetrahydro-benzothiazole-6-carboxylic acid	C16H19N5O3S 361.4	1.46 (LC-2)	316.25/314.15
C-47		N-(tetrahydro-benzothiazole-2-yl-4-spiro-cyclohexane)-guanidine	spiro[5.5]undec-an-1-one	C13H20N4S 264.4	1.69 (LC-2)	265.63/263.24
C-48		N-(6-phenyl-4,5,6,7-tetra-hydro-benzo-thiazol-2-yl-4-spiro-cyclohexane)-guanidine hydrobromide	4-phenyl-spiro[5.5]undec-an-1-one	C19H25BrN4S 421.4	1.85 (LC-2)	341.54/339.24

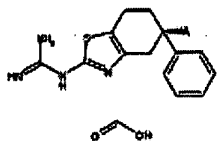
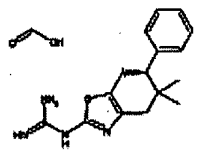
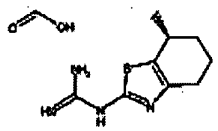
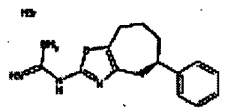
Example	Structure	Name	Starting product	Empirical formula Molecular weight	t_R [min] (HPLC method)	MS data *m/z* $[M+H]^+/[M-H]^-$
C-49		N-(6,6-diphenyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine formate	4,4-diphenyl-cyclohexanone	C21H22N4O2S 394.5	3.15 (LC-1)	349.24/347.44
C-50		2-guanidino-6-phenyl-4,5,6,7-tetrahydro-benzo-thiazol-6-carboxylic acid-ethyl ester formate	4-oxo-1-phenyl-cyclohexane carboxylic acid ethyl ester	C18H22N4O4S 390.5	1.75 (LC-2)	345.36
C-51		N-(6-cyano-6-phenyl-4,5,6,7-tetrahydro-benzo-thiazol-2-yl)-guanidine hydrobromide	4-cyano-4-phenylcyclo-hexanone	C15H16BrN5S 378.3	2.92 (LC-1)	298.1/295.97
C-52		N-[6-(4-methoxy-phenyl)-4,5,6,7-tetrahydro-benzo-thiazol-2-yl]-guanidine hydrobromide	4-(4-methoxy-phenyl)cyclo-hexanone	C15H19BrN4OS 383.3	3.0 (LC-1)	303.25/301.26

Example	Structure	Name	Starting product	Empirical formula Molecular weight	t_R [min] (HPLC method)	MS data *m/z* $[M+H]^+$/ $[M-H]^-$
C-53		N-[6-(4-benzyloxy-phenyl)-4,5,6,7-tetrahydro-benzothiazole-2-yl]-guanidine hydrobromide	4-(4-benzyl-oxyphenyl)cyclo-hexanone	C21H23BrN4OS 459.4	3.24 (LC-1)	379.26
C-54		N-[6-(4-fluorophenyl)-4,5,6,7-tetrahydro-benzo-thiazol-2-yl]-guanidine hydrobromide	4-(4-fluorophenyl)-cyclo-hexanone	C14H16BrFN4S 371.3	3.04 (LC-2)	291.26/289.33
C-55		N-(6-o-tolyl-4,5,6,7-tetrahydro-benzo-thiazol-2-yl)-guanidine formate	4-0-tolyl-cyclohexanone	C16H20N4O2S 332.4	3.42 (LC-2)	286.25
C-56		N-[6-(2-ethyl-phenyl)- 4,5,6,7-tetrahydro-benzo-thiazol-2-yl]-guanidine formate	4-(2-ethyl-phenyl)-cyclo-hexanone	C17H22N4O2S 346.4	3.13 (LC-2)	301.33/299.4

Example	Structure	Name	Starting product	Empirical formula Molecular weight	t_R [min] (HPLC method)	MS data *m/z* $[M+H]^+$/ $[M-H]^-$
C-57		N-[6-(3,4-dimethoxyphenyl)-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine formate	4-(3,4-dimethoxy-phenyl)cyclo-hexanone	C17H22N4O4S 378.4	3.44 (LC-2)	333.2
C-58		N-[6-(4-cyanophenyl)-4,5,6,7-tetrahydro-benzo-thiazol-2-yl]-guanidine formate	4-(4-oxo-cyclohexyl)-benzonitrile	C16H17N5O2S 343.4	1.59 (LC-2)	298.17/296.26
C-59		N-[6-(3,5-bis-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-benzo-thiazol-2-yl)-guanidine formate	4-(3,5-bis-trifluoromethyl-phenyl)-cyclo-hexanone	C17H16F6N4O2S 454.4	1.88 (LC-2)	408.99/407.15
C-60		N-(6-p-tolyl-4,5,6,7-tetrahydro-benzo-thiazol-2-yl)-guanidine formate	4-p-tolyl-cyclohexanone	C16H20N4O2S 332.4	1.68 (LC-2)	287.15

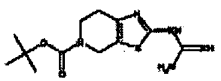
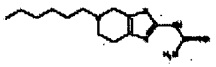
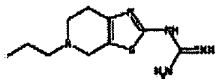
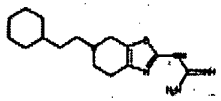
Example	Structure	Name	Starting product	Empirical formula Molecular weight	t_R [min] (HPLC method)	MS data *m/z* $[M+H]^+$/ $[M-H]^-$
C-61		N-(6-m-tolyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine formate	3-m-tolyl-cyclohexanone	C16H20N4O2S 332.4	1.73 (LC-2)	287.22
C-62		N-[6-(3-methoxy-phenyl)-4,5,6,7-tetrahydro-benzo-thiazol-2-yl]-guanidine formate	4-(3-methoxy-phenyl)cyclo-hexanone)	C16H20N4O3S 348.4	1.73 (LC-2)	303.2/301.35
C-63		N-[6-(4-chloro-phenyl)-4,5,6,7-tetrahydro-benzo-thiazol-2-yl]-guanidine formate	4-(4-chloro-phenyl)-cyclohexanone	C15H17ClN4O2S 352.8	1.85 (LC-2)	307.15/305.13
C-64		N-[6-(3-fluorophenyl)-4,5,6,7-tetrahydro-benzo-thiazol-2-yl]-guanidine formate	4-(3-fluorophenyl)-cyclohexanone	C15H17FN4O2S 336.4	1.55 (LC-2)	290.91/289.25

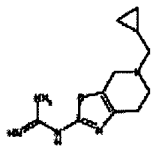
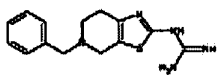
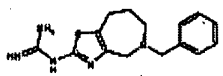
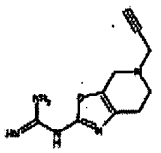
Example	Structure	Name	Starting product	Empirical formula Molecular weight	t_R [min] (HPLC method)	MS data *m/z* $[M+H]^+$/ $[M-H]^-$
C-65		N-(6-thiophene-2-yl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine formate	4-thiophene-2-yl-cyclohexanone	C13H16N4O2S2 324.4	1.61 (LC-2)	279.13/277.22
C-66		N-(6-benzo[1,3]-dioxol-5-yl-4-4,5,6,7-tetrahydro-benzo-thiazol-2-yl)-guanidine formate	4-benzo[1,3]dioxol-5-yl-cyclo-hexanone	C16H18N4O4S 362.4	1.66 (LC-2)	317.02
C-67		N-(5,5-dimethyl-4,5,6,7-tetrahydro-benzo-thiazol-2-yl)-guanidine formate	3,3-dimethyl-cyclohexanone	C11H18N4O2S 270.3	2.92 (LC-2)	225.34
C-68		N-(5-ethyl-5-methyl- 4,5,6,7-tetrahydro-benzo-thiazol-2-yl]-guanidine formate	3-ethyl-3-methyl-cyclohexanone	C12H20N4O2S 284.4	2.97 (LC-1)	239.25/237.2

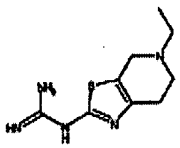
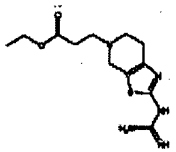
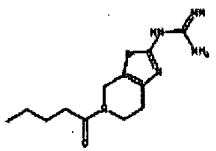
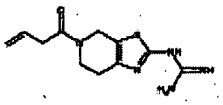
Example	Structure	Name	Starting product	Empirical formula Molecular weight	t_R [min] (HPLC method)	MS data *m/z* $[M+H]^+$/ $[M-H]^-$
C-69		N-(5-methyl-5-phenyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine formate	3-methyl-3-phenyl-cyclohexanone	C16H20N4O2S 332.4	3.01 (LC-2)	286.45
C-70		N-(5,5-dimethyl-6-phenyl-4,5,6,7-tetrahydro-benzo-thiazol-2-yl]-guanidine formate	3,3-dimethyl-4-phenyl-cyclohexanone	C17H22N4O2S 346.4	1.85 (LC-2)	301.33/299.35
C-71		N-(7-methyl-4,5,6,7-tetrahydro-benzo-thiazol-2-yl)-guanidine formate	2-bromo-3-methyl-cyclohexanone	C10H16N4O2S 256.3	2.84 (LC-1)	211.24
C-72		N-(5-phenyl-5,6,7,8-tetrahydro-4H-cycloheptathiazol-2-yl]-guanidine hydrobromide	2-bromo-6-phenyl-cycloheptanone	C15H19BrN4S 367.3	3.05 (LC-2)	287.34/285.42

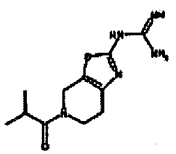
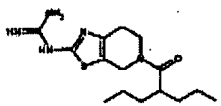
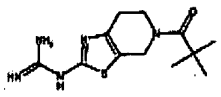
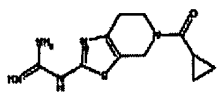
Example	Structure	Name	Starting product	Empirical formula Molecular weight	t_R [min] (HPLC method)	MS data *m/z* $[M+H]^+$ / $[M-H]^-$
C-73		N-(4-*tert*-butyl-6-phenyl-4,5,6,7-tetrahydro-benzothiazole-2-yl)-guanidine	2-*tert*-butyl-6-chloro-4-phenyl-cyclohexanone	C18H24N4S 328.5	1.85 (LC-2)	329.25/327.27

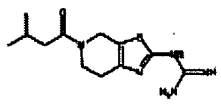
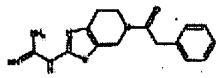
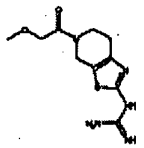
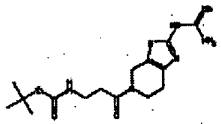
Table 4: Analytical data for Examples N-01 to N-33

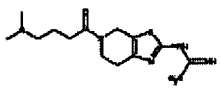
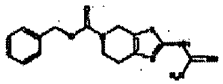
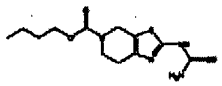
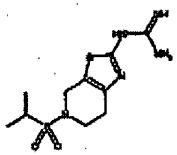
Example	Structure	Name	R'-reagent	Empirical formula Molecular weight	t_R [min] (HPLC method)	MS data *m/z* $[M+H]^+$/ $[M-H]^-$
N-01		2-guanidino-6,7-dihydro-4*H*-thiazolo[5,4-c] pyridine-5-carboxylic acid tert-butyl ester		C12H19N502S 297.4	2.88 (LC-1)	298.22/296.29
N-02		N-(5-hexyl-4,5,6,7-tetrahydro-thiazolo[5,4-c] pyridine-2-yl)-guanidine	1-bromohexane	C13H23N5S 281.4	0.94 (LC-1)	282.18/280.33
N-03		N-(5-propyl-4,5,6,7-tetrahydro-thiazolo[5,4-c] pyridine-2-yl)-guanidine	1-bromopropane	C10H17N5S 239.3	0.85 (LC-1)	240.18/238.31
N-04		N-[5-(2-cyclohexyl-ethyl-4,5,6,7-tetra-hydro-thiazolo [5,4-c]pyridine-2-yl)-guanidine	(2-bromethyl)-cyclohexane	C15H25N5S 307.5	0.95 (LC-1)	308.28/306.42

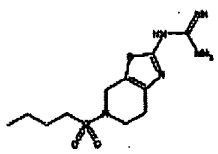
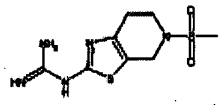
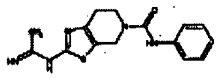
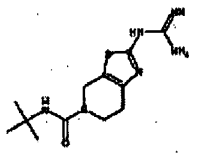
Example	Structure	Name	R'-reagent	Empirical formula Molecular weight	t_R [min] (HPLC method)	MS data *m/z* $[M+H]^+$/ $[M-H]^-$
N-05		N-(5-cyclo-propylmethyl-4,5,6,7-tetrahydro-thiazolo[5,4-c] pyridine-2-yl)-guanidine	bromomethyl-cyclopropane	C11H17N5S 251.3	0.86 (LC-1)	252.16/250.25
N-06		N-(5-benzyl-4,5,6,7-tetrahydro-thiazolo[5,4-c] pyridine-2-yl)-guanidine	benzyl bromide	C14H17N5S 287.4	2.67 (LC-1)	288.22/286.16
N-07		N-(5-benzyl-5,6,7,8-tetrahydro-4*H*-thiazolo[4,5-c] azepine-2-yl)-guanidine	benzyl bromide	C15H19N5S 301.4	0.9 (LC-1)	302.12/300.02
N-08		N-(5-prop-2-ynyl-4,5,6,7-tetra-hydro-thiazolo [5,4-c]pyridine-2-yl)-guanidine	propargyl bromide	C10H13N5S 235.3	0.83 (LC-1)	236.16/234.25

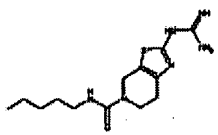
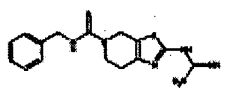
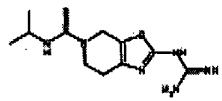
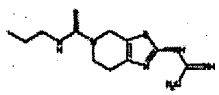
Example	Structure	Name	R'-reagent	Empirical formula Molecular weight	t_R [min] (HPLC method)	MS data *m/z* $[M+H]^+$/ $[M-H]^-$
N-09		N-(5-ethyl-4,5,6,7-tetrahydro-thiazolo[5,4-c] pyridine-2-yl)-guanidine	1-bromomethane	C9H15N5S 225.3	0.86 (LC-1)	226.20/227.07
N-10		3-(2-guanidino-6,7-dihydro-4H-thiazolo[5,4-c] pyridine-5-yl)-propionic acid ethyl ester	ethyl-3-bromopropionate	C12H19N502S 297.4	0.84 (LC-1)	298.18/296.35
N-11		N-(5-pentanoyl-4,5,6,7-tetrahydro-thiazolo[5,4-c] pyridine-2-yl)-guanidine	pentanoyl chloride	C12H19N5OS 281.4	2.46 (LC-1)	282.21/280.32
N-12		N-(5-but-3-enoyl-4,5,6,7-tetra-hydro-thiazolo [5,4-c]pyridine-2-yl)-guanidine	vinylacetic acid	C11H15N5OS 265.3	0.82 (LC-1)	266.21/264.29

Example	Structure	Name	R'-reagent	Empirical formula Molecular weight	t_R [min] (HPLC method)	MS data *m/z* $[M+H]^+$/ $[M-H]^-$
N-13		N-(5-isobutyryl-4,5,6,7-tetrahydro-thiazolo[5,4-c] pyridine-2-yl)-guanidine	isobutyryl chloride	C11H17N5OS 267.3	0.81 (LC-1)	268.20/266.32
N-14		N-[5-(2-propyl-pentanoyl)-4,5,6,7-tetrahydro-thiazolo[5,4-c] pyridine-2-yl)-guanidine	2-propyl-pentanoyl-chloride	C15H25N50S 323.5	2.56 (LC-1)	324.28/322.31
N-15		N-[5-(2,2-dimethyl-propionyl)-4,5,6,7-tetrahydro-thiazolo[5,4-c] pyridine-2-yl)-guanidine	2,2-dimethyl-propionyl chloride	C12H19N5OS 281.4	2.47 (LC-1)	282.18/280.31
N-16		N-(5-cyclopropane-carbonyl-4,5,6,7-tetrahydro-thiazolo [5,4-c]pyridine-2-yl)-guanidine	Cyclopropane-carbonyl chloride	C11H15N5OS 265.3	0.82 (LC-1)	266.19/264.24

Example	Structure	Name	R'-reagent	Empirical formula Molecular weight	t_R [min] (HPLC method)	MS data *m/z* $[M+H]^+$/ $[M-H]^-$
N-17		N-[5-(3-methyl-butyryl)-4,5,6,7-tetrahydro-thiazolo[5,4-c] pyridine-2-yl)-guanidine	3-methyl-butyryl chloride	C12H19N5OS 281.4	0.83 (LC-1)	282.25/280.33
N-18		N-[5-(2-phenlacetyl-4,5,6,7-tetrahydro-thiazolo[5,4-c] pyridine-2-yl)-guanidine	phenylacetyl chloride	C15H17N50S 315.4	2.49 (LC-1)	316.15/314.25
N-19		N-[5-(2-methoxy-acetyl)- 4,5,6,7-tetrahydro-thiazolo[5,4-c] pyridine-2-yl]-guanidine	methoxyacetic acid	C10H15N5O2S 269.3	0.83 (LC-1)	270.20/268.34
N-20		[3-(2-guanidino-6,7-dihydro-4H-thiazolo[5,4-c] pyridine-5-yl)-3-oxo-propyl]carbamic acid tert-butylester	boc-beta-alanine	C15H24N6O3S 368.5	0.81 (LC-1)	369.13/367.27

Example	Structure	Name	R'-reagent	Empirical formula Molecular weight	t_R [min] (HPLC method)	MS data *m/z* $[M+H]^+$/ $[M-H]^-$
N-21		N-[5-(4-dimethylamino-butyryl)-4,5,6,7-tetrahydro-thiazolo[5,4-c] pyridine-2-yl)-guanidine	4-dimethylamino butanoic acid	C13H22N6OS 310.4	0.82 (LC-1)	311.16/309.15
N-22		2-guanidino-6,7-dihydro-4H-thiazolo[5,4-c] pyridine -5-carboxylic acid benzyl ester	benzyl chloroformate	C15H17N5O2S 331.4	2.7 (LC-1)	332.17/330.24
N-23		2-guanidino-6,7-dihydro-4H-thiazolo[5,4-c] pyridine -5-carboxylic acid butyl ester	butyl chloroformate	C12H19N5O2S 297.4	2.67 (LC-1)	298.25/296.28
N-24		N-[5-(propane-2-sulphonyl)-4,5,6,7-tetrahydro-thiazolo[5,4-c] pyridine-2-yl)-guanidine	2-propanesulphonyl chloride	C10H17N5O2S2 303.4	0.81 (LC-1)	304.08/302.25

Example	Structure	Name	R'-reagent	Empirical formula Molecular weight	t_R [min] (HPLC method)	MS data *m/z* $[M+H]^+$/ $[M-H]^-$
N-25		N-[5-(butane-1-sulphonyl)- 4,5,6,7-tetrahydro-thiazolo[5,4-c] pyridine-2-yl)-guanidine	1-butanesulphonyl chloride	C11H19N5O2S2 317.4	0.84 (LC-1)	318.11/316.28
N-26		N-(5-methanesulphonyl-4,5,6,7-tetrahydro-thiazolo[5,4-c] pyridine-2-yl)-guanidine	methanesulphonyl chloride	C8H13N502S2 275.3	0.83 (LC-1)	267.11/274.25
N-27		2-guanidino-6,7-dihydro-4H-thiazolo[5,4-c] pyridine-5-carboxylic acid phenyl amide	phenyl isocyanate	C14H16N6OS 316.4	2.76 (LC-1)	317.19/315.33
N-28		2-guanidino-6,7-dihydro-4H-thiazolo[5,4-c] pyridine -5-carboxylic acid *tert*-butyl amide	tert-butyl isocyanate	C12H20N6OS 296.4	2.73 (LC-1)	297.25/295.4

Example	Structure	Name	R'-reagent	Empirical formula Molecular weight	t_R [min] (HPLC method)	MS data *m/z* $[M+H]^+$/ $[M-H]^-$
N-29		2-guanidino-6,7-dihydro-4*H*-thiazolo[5,4-c] pyridine -5-carboxylic acid pentyl amide	pentyl isocyanate	C13H22N6OS 310.4	2.81 (LC-1)	311.23/309.37
N-30		2-guanidino-6,7-dihydro-4*H*-thiazolo[5,4-c] pyridine -5-thiocarboxylic acid benzyl amide	benzylamine	C15H18N6S2 346.5	2.91 (LC-1)	246.82/345.09
N-31		2-guanidino-6,7-dihydro-4H-thiazolo[5,4-c] pyridine -5-thiocarboxylic acid isopropyl amide	isopropylamine	C11H18N6S2 298.4	2.94 (LC-1)	298.86/296.29
N-32		2-guanidino-6,7-dihydro-4H-thiazolo[5,4-c] pyridine -5-thiocarboxylic acid propylamide	propylamine	C11H18N6S2 298.4	2.78 (LC-1)	299.11/291.7

Example	Structure	Name	R'-reagent	Empirical formula Molecular weight	t_R [min] (HPLC method)	MS data *m/z* $[M+H]^+$/ $[M-H]^-$
N-33		2-guanidino-6,7-dihydro-4*H*-thiazolo[5,4-c] pyridine -5-thiocarboxylic acid-(2-methoxy-1-methyl-ethyl) amide	2-amino-1-methoxypropane	C12H20N6OS2 328.4	2.72 (LC-1)	329.38/326.93